NDT Plus (2008) 4: 199–205
doi: 10.1093/ndtplus/sfn074

NDT PLUS
Nephrology Dialysis Transplantation

In-Depth Clinical Review

Left ventricular dysfunction in the haemodialysis population

Manish M. Sood[1], Robert P. Pauly[2], Claudio Rigatto[1] and Paul Komenda[1]

[1]St Boniface General Hospital and the University of Manitoba, Winnipeg, Manitoba, Canada and [2]Edmonton General Hospital, University of Alberta, Edmonton, Alberta, Canada

Abstract

Cardiovascular disease in the haemodialysis population continues to contribute to mortality and morbidity. Disorders of left ventricular geometry and function are highly prevalent and lead to increased mortality in this highly vulnerable population. Left ventricular dysfunction (LVDys), often as a result of hypertension, ischaemic cardiac disease or dilated cardiomyopathy, has not been uniformly defined in the literature making diagnosis and therapy problematic. Although routinely available, screening by echocardiography is critically volume dependent and prone to underestimation in left ventricular ejection fraction. Few randomized control trials are available to guide management with the majority of evidence requiring extrapolation from the non-dialysis population. Beyond medication, interventional cardiac procedures such as implantable cardiac defibrillator implantation and cardiac resynchronization therapy show promise. Conversion to alternative dialysis modalities such as peritoneal dialysis, short-daily or nocturnal dialysis have been attempted and are actively being explored.

Keywords: beta blockers; cardiac defibrillators; haemodialysis; left ventricular dysfunction; nocturnal haemodialysis

Left ventricular dysfunction in the haemodialysis population

Cardiovascular disease remains the primary culprit for poor health outcomes and high mortality in patients undergoing maintenance dialysis. In the haemodialysis (HD) population left ventricular dysfunction (LVDys) is common with a rate 10–30 times greater than that in the general population [1–4]. The clinical diagnosis of congestive heart failure (CHF) in the HD population, which may be due to decreased left ventricular function, correlates strongly with mortality, having a reported 3-year survival of only 17% [5]. LVDys is often preceded by left ventricular hypertrophy (LVH) that in itself carries a poor prognostic value for mortality in patients with ESRD [6–10]. Taken together, LVDys (or its precursor, LVH) and its clinical correlate, CHF, confer a substantially increased risk of morbidity and mortality. These links are significant enough for National Kidney Foundation guidelines to recommend baseline and routine echocardiographic follow-up for all patients initiating dialysis [11].

The literature concerning disorders of left ventricular (dys)function in HD can be daunting since there is no uniform definition of the problem, multiple aetiologies exist and several methods of measurement are employed, making comparisons of individual studies difficult to interpret. For clarity, we will define LVDys as a left ventricular ejection fraction <40% or endocardial left ventricular shortening <25% [12]. LVH is categorically defined as left ventricular mass index (LVMI) of >131 g/m^2 in males and >100 g/m^2 in females taken from the upper limits of normal used in the Framingham Study [13]. LVMI is simply the LVM normalized to body surface area. CHF is a clinical diagnosis based on the presence of dyspnoea and pulmonary oedema that may or may not involve LVDys. This review will focus on various aspect of LV systolic dysfunction in the HD population. The incidence and prevalence, methods of measurement, pharmacological and interventional management, and alternative dialytic treatment strategies will be discussed.

Incidence, prevalence and mortality of LV dysfunction in haemodialysis patients

Early seminal studies by Foley *et al*. of 432 dialysis patients studied prospectively in the 1980s focused on distortions of left ventricular architecture, namely LVH, and clinical CHF [9,14–18]. They reported high rates of 75% and 31% of patients who had LVH and CHF at initiation of dialysis, respectively [14,16]. Furthermore, prevalent HD patients had rates of *de novo* CHF of 25% [17]. It seemed that left ventricular disorders were common in the HD patient population. This observation was solidified by other investigators who reported rates of 46–79% for LVH and 13–36% for LV systolic dysfunction [19–22]. Key studies reporting

Correspondence and offprint requests to: Manish M. Sood, Section of Nephrology, Manitoba Renal Program, St Boniface Hospital, 409 Tache Avenue, Winnipeg, Manitoba, R2H 2A6, Canada. Tel: +1-204-235-3450; Fax: +1-204-233-2770; E-mail: msood@sbgh.mb.ca; msood99@gmail.com

Table 1.

Author/year	Study type	Key findings (pertaining to systolic dysfunction)	Imaging/definition of LV dysfunction	Considerations
Greaves *et al*. 1994 [21]	84 prevalent patients (mean = 3.9 years on HD/CAPD)	36% systolic dysfunction	Echocardiography (FS ≤ 25%)	Mean HCT 0.28, no report of CHF med use
Foley, Parfrey, Harnett *et al*. [9,14,15,17,18]	432 patients prospective over 41 months	LV dysfunction but not LVMI predicts CHF	Echocardiography (FS ≤ 25%)	Mean haemoglobin 8.7 g/dL, no report of CHF med use
Joki *et al*. 2003 [20]	88 incident HD patients followed for 3 years	27% had systolic dysfunction that predicted cardiac death	Echocardiography (EF≤50%)	
Mallamaci *et al*. 2001 [19]	246 prevalent patients (HD/PD). No clinical CHF. Biomarker study	79% LVH 13% systolic dysfunction	Echocardiography (LVEF ≤ 45%)	Minimal use of ACE/ARB/B-blockers/EPO Hgb not reported
Zoccali *et al*. 2000 [8]	254 prevalent patients (HD/PD)	77% LVH 22% systolic dysfunction by LVEF measurement 48% systolic dysfunction by midwall fractional shortening	Echocardiography (LVEF < 50%, fractional shortening <28%)	No report of CHF med use

rates of incidence and/prevalence of left ventricular disorders in HD patients are summarized in Table 1.

Does LV systolic dysfunction confer an adverse prognosis? Foley *et al*. utilized a multivariate model to predict that the significant risk factors for recurrent CHF were ischaemic heart disease (RR 3.10), anaemia (RR 1.25/10 g fall), hypoalbuminaemia (1.37/5 g fall) and baseline systolic dysfunction on echocardiogram (1.92). As expected, systolic dysfunction at baseline was the strongest predictor of CHF presence at the initiation of dialysis (OR 5.34). LVMI (per 20 g/m^2) was not a significant predictor of CHF at baseline or recurrence in this cohort. In a separate report using the same cohort of patients, Parfrey *et al*. report that the mean time to death in patients with systolic dysfunction was 38 months [18]. Joki *et al*. showed a positive predictive value of 42% for cardiac death within 3 years if a patient had an EF ≤ 50% [19].

It may be difficult to generalize many of these earlier epidemiologic studies in CHF to the modern era due to more ubiquitous use of evidence-based approaches to treatment of CHF. Specifically, renin–angiotensin system inhibition, B-blockers and strict blood pressure control have all been shown to abrogate the natural history of CHF in ESRD patients [23,24], although the penetrance of all of these interventions in ESRD populations is likely quite centre dependent [23].

A second difficulty in generalizing earlier studies to modern day care involves the fact that LVH clearly begins before patients reach the need for dialysis as reported by Levin *et al*. in two separate CKD study populations [25,26]. These reports associate elevated systolic blood pressure and lower haemoglobin with LVH. It appears that regression of LVMI can occur with anaemia correction in CKD populations [27,28]; however, the normalization of haemoglobin in dialysis patients does not seem to impact on LVH [29] and, in fact, may lead to increased mortality in certain groups of patients [30].

A further caveat in gauging prevalence of systolic dysfunction in this population surrounds the heterogeneity in cutoffs for what entails 'dysfunction'. Current recommendations for the classification of EF are mild dysfunction 41–49%, moderate 35–40% and <35% severe [31]. The large cohort study by Parfrey *et al*. [18] used a cutoff ejection fraction of 25% versus the Mallamaci *et al*. [19] study that uses 40%. Despite this, the Parfrey group reports a higher prevalence of systolic dysfunction at 16% versus 13% by Mallamaci *et al*. These contradictory results may be explained by the timing of the echocardiogram. In the Mallamaci cohort the echo was performed midweek whereas in the Parfrey cohort, the echo timing was not specified and may have been predialysis.

Era effects, assorted study conditions and heterogeneous definitions of 'systolic dysfunction' render inter-study generalizations about exact numbers of incidence and prevalence for cardiac dysfunction problematic. Information bias (see the next section) further worsens the issue of comparison. Taking all of these factors into consideration, the fact remains that echocardiographic evidence of LVDys and LVH remain important prognostic indicators for predicting cardiac demise in the dialysis population.

Methods of measurement

Information bias can occur when there is a random or systematic inaccuracy in measurement. Unfortunately, the most widely used means of measurement of left ventricular function, M mode, two-dimensional echocardiography is prone to significant information bias. While its benefits include wide availability, relatively low cost and good inter-observer reliability [32], errors may occur because many of the measurements are based on geometric assumptions. The calculated left ventricular mass (LVM) relies heavily on the measurement of left ventricular internal dimension (LVID) that, in turn, is susceptible to changes with plasma volume [33]. Thus, sensitivity to volume status at the time of measurement is crucial in obtaining an accurate measure. Failure to obtain a true dry weight or echocardiographic assessment prior to HD will lead to underestimations of LV function. In two small series, the average reductions

in LVMI and end-diastolic diameter from pre- to post-dialysis were 26.2–36.1 g/m^2 and 4–8.4 mm, respectively [34,35].

From the nephrologists' perspective, newer techniques of visualization of cardiac structures are emerging that may minimize information bias. In experimental settings, cardiac magnetic resonance imaging (MRI) is becoming more readily available and directly measures cardiac mass, thereby circumventing the geometric assumptions and calculations used in echocardiography. Indeed in head to head comparisons of cardiac MRI versus echocardiography, MRI detected lower LV mass (122.3 versus 177 g/m^2 for men, 133.5 versus 89.6 g/m^2 for women) and better intra-observer variability (4.3% versus 9.6%) [36]. Of note, the same study found that as left ventricular dilatation increased, so did the overestimation of LV mass by echocardiography. Cardiac MRI is greatly limited by cost, availability, claustrophobia, contraindications such as pacemakers and, lastly, concerns with gadolinium use and its association with nephrogenic systemic fibrosis. Thus, cardiac MRI is still used primarily in the experimental setting.

Real-time 3D echocardiography (RT3DE) and cardiac CT (CCT) are potential future modalities for cardiac structural assessment. RT3DE, when compared to 2D echocardiography, can be performed without geometric modelling, thereby foregoing the need for error magnifying calculations [37]. In direct comparisons, RT3DE has better correlation with cardiac MRI versus CCT (r^2 = 0.93 versus 0.85) for measurements of ejection fraction and less bias by the Bland–Altman analysis (0.3% versus −2.8%) but a higher rate of intra- and interobserver variability.

With cardiac MRI as the gold standard for cardiac structure, positron emission tomography (PET) is considered the gold standard for cardiac tissue perfusion. Preliminary studies have shown PET imaging to be highly sensitive and specific in detecting regional wall motion abnormalities and changes in myocardial blood flow during haemodialysis [38]. Future studies combining the two techniques could elucidate myocardial perfusion in the dilated ventricular and its response to various pharmacologic and interventional therapies.

Pharmacological management of LVDys in HD

A paucity of literature exists on the use of pharmacological agents in HD patients with LVDys as often elevations in creatinine and the presence of ESRD are used as exclusion criteria. Discussions regarding the extrapolation of evidence for usage of pharmacologic therapy have been recently reviewed elsewhere [20,39]. To date, only a few small randomized studies have shown pharmacologic benefit in HD patients in prevention of CHF and established LVDys.

The strongest evidence of benefit exists for the utilization of beta-blockers. A small open-label RCT examined the effect of carvedilol versus placebo on cardiovascular disease in dialysis patients with symptomatic, NYHA Class 2 or higher CHF and echocardiographic evidence of impaired left ventricular systolic function (ejection fraction <35%). The investigators showed improvement in clinical NYHA class and ejection fraction in the carvedilol group at 1 year [40]. Based on these favourable findings, the protocol was continued for another year at which point an impressive 50% relative risk reduction (RRR) in all cause death, a 55% RRR in hospitalization and a 68% RRR in cardiovascular death were observed with carvedilol [41]. While these results are broadly congruent with the previously cited observational data and with the known benefit of BB in non-dialysis patients with CHF, several methodological concerns have been raised, including a small and possibly non-representative patient sample characterized by an unusually high mortality rate (70% at 2 years in the placebo group) and an open label design. Nevertheless, the data presented do support the use of carvedilol in a small subset of haemodialysis patients with symptomatic dilated cardiomyopathy (NYHA 2 or 3 heart failure and EF <35%). Whether the benefits observed can be generalized to other BB, to peritoneal dialysis patients, or to patients without symptomatic heart failure or dilated cardiomyopathy will need to be addressed in future.

Angiotensin blocking agents are a mainstay of therapy of LVDys in the non-dialysis population; however, their role in the HD population appears much less clear. Evaluation of the evidence is hampered by the lack of studies stratifying HD patients according to the presence of LVDys. Several studies have documented a favourable effect on surrogate outcomes. RAS antagonists are effective in reducing hypertension, regressing LVH, improving large vessel compliance and preserving residual renal function in dialysis patients [42–45]. One randomized controlled trial (RCT) by Zannad *et al*. examined the effect of fosinopril on the reduction of cardiovascular events (CVE) in 397 dialysis patients with LVH [46]. A 7% reduction in CVEs was observed, but it was not statistically significant due to the low statistical power of the study. The composite endpoint of CVE included CHF requiring hospitalization (6% of the total who reached primary endpoint); however, it is unclear whether fosinopril truly confers any benefit. In a small RCT, candasartan therapy resulted in CVE of 16.3% versus 45.9% in those not treated ($P < 0.01$) [47]. At baseline, the average LVEF was 61 ± 2.8% in the treatment arm with 5/43 patients reaching the endpoint of CHF requiring hospitalization versus 11/37 patients in the control arm. In a small, single centre RCT, ARB therapy appears to decrease *de novo* CHF in patients with normal ejection fraction at baseline. Whether ACEI or ARB improves prevalent LVDys, mortality or morbidity remains unknown.

More recently, data in dialysis patients and the general population have suggested that ASA use may be associated with increased risk of *de novo* and recurrent heart failure [48,49]. This effect persisted even after adjustment for other risk factors including prevalent CAD. Important limitations to this data include the observational design of the studies, which cannot establish causation, and the problem of residual confounding due to incomplete adjustment for the effect of confounding variables. Nevertheless, these findings remain a concern, because heart failure is a major mechanism of death in dialysis patients, and so a negative

impact on this event could diminish the overall benefit of ASA in preventing death.

Interventional management

Left ventricular dysfunction is associated with sudden cardiac death and one quarter of all cardiac deaths in HD patients are due to arrthymogenic sudden cardiac death [50]. However, the role of ICD implantation in haemodialysis patients with left ventricular dysfunction has not been well established [51]. Current recommendations by the American College of Cardiology state that ICDs should be used as primary prevention in patients with good functional capacity, an EF <30% with mild to moderate symptoms of heart failure and expected survival to be >1 year (level of evidence B) [52]. The role of ICD insertion for primary prevention in patients with EF 30–40% is, in general, much more controversial; however, patients post-ACS with non-sustained ventricular tachycardia or significant symptoms appear to benefit (level of evidence B) [3]. A reasonable number of dialysis patients with severe reductions in EF can be expected to survive >1 year. In the trial by Cice *et al*, the 2-year mortality for patients with an average EF of 26% on carvedilol was found to be 52% [41]. Using an EF <30% as criteria for ICD implantation in HD patients may be too stringent a criterion as HD patients suffer higher event rates compared to the general population and thereby may benefit the most by their use. As secondary prevention, ICD use appears to be beneficial as Herzog *et al*. showed a 42% relative risk reduction [RR 0.58 (95% CI 0.50, 0.66)] with ICD implantation in HD patients [53]. Ejection fraction was not available as the data were derived from Medicare claims. Furthermore it appears that ICD usage in HD patients is underutilized as only 8% of eligible HD patients in Herzog's study received an ICD as secondary prevention. In a small, single-centre study, 8 of 46 (17%) patients with an EF <40% had an ICD implantation; however, indications for ICD insertion were not provided. To date, there are no randomized studies looking at the benefit of ICD implantation as either primary or secondary prevention in HD patients with LVDys.

Cardiac resynchronization (CRT) with or without ICD implantation is being more frequently utilized for heart failure management in select populations. CRT involves the use of a specialized pacemaker to resynchronize the actions of the left and right ventricle. Benefits include improvements in quality of life, EF, functional class and survival [54,55]. Indications for implantation include EF <35%, a QRS interval of 130 ms and persistent symptoms. Currently no studies have delineated the potential role of CRT in the HD population. A *post hoc* analysis of the COMPANION trial, found among patients who underwent cardiac resynchronization, that renal dysfunction was associated with an increased risk of sudden cardiac death [HR 1.69 (95% CI 1.06–2.69)] but whether this pertains to the ESRD population remains unknown [56]. CRT seems like a viable treatment option in suitable patients with HD; however, studies of clinical outcomes are lacking.

Underutilization of interventional cardiology procedures on HD patients is likely related to under-referral and an increase in complication rate. There is no literature on underutilization in HD; however, the suspicion exists [57]. Increased rates of complication have been shown by Dasgupta *et al*. They conducted a retrospective, single-centre study finding an overall complication rate of 39% in ESRD patients versus 11% for controls ($P < 0.001$) [58]. Haematomas, thrombosis and other device-related complications were more common in the ESRD group while infection rates were not statistically different. Of note, thrombosis to an access graft or fistula occurred in 3/6 patients when the device was placed ipsilateral and 19% when placed contra lateral to the access. Dialysis patients were more likely to have diabetes, hypertension, low albumin and a higher INR versus controls partially explaining these results. Insertion of these devices requires contrast administration for adequate visualization that may damage residual renal function. Overall, complication rates appear to be higher, albeit with a paucity of data on the subject, in HD patients requiring cardiovascular intervention. A careful risk versus benefit assessment in individual patients should guide therapeutic decision making.

Alternative dialysis modalities

Hypotension and inability for adequate ultrafiltration often limit effective intermittent haemodialysis therapy with LVDys. This has lead to the exploration of alternative dialysis modalities and techniques.

Peritoneal dialysis

Advocates of peritoneal dialysis (PD) have long suggested that this modality is better suited to manage patients with LVDys on account of its continuous, gentle ultrafiltration that avoids the significant haemodynamic fluctuations associated with conventional haemodialysis. However, the validity of this assumption is likely confounded by an era effect, the influence of residual renal function, the type of PD performed (i.e. continuous ambulatory peritoneal dialysis, automated peritoneal dialysis or a hybrid approach) and the choice of dialysate (dextrose only versus dextrose plus icodextrin). To our knowledge there are no randomized controlled trials comparing PD to conventional haemodialysis in the management of CHF or asymptomatic LVDys. Data from a large observational cohort of >100 000 incident ESRD patients between 1995 and 1997 suggest that mortality is actually higher for PD-treated patients with CHF and gets worse with increasing duration of follow-up [59]. This may be related to declining residual renal function, inadequate ultrafiltration with changing membrane characteristics over time or some other PD-specific factor. In fact, sub-clinical overhydration is more common in PD than originally thought and certainly more pronounced than in haemodialysis patients or renal transplant recipients [60,61]. This subtle but significant expansion of extracellular fluid volume in PD is associated with hypertension and left ventricular hypertrophy (LVH), both of which are determinants of LVDys [61,62]. Notwithstanding these findings, good volume and blood pressure control is achievable in the modern PD era with liberal use of icodextrin and hypertonic

dialysate resulting in stabilization of LVH [63,64]. However, it appears that this occurs at the expense of residual renal function and whether the latter offsets the presumed cardiac benefits is not known. In light of this observational evidence, no definitive statement concerning the preferential use of PD in the management of LVDys in ESRD can be made.

New dialysis strategies

Patients undergoing short daily haemodialysis (SDHD) usually receive 1.5–2.5 h of dialysis 5–6 days per week. In comparison to three times per week conventional haemodialysis, SDHD is consistently associated with a decrease in blood pressure, antihypertensive use and LVMI [65,66]. The mechanism underlying this improvement is likely multifactorial but reduced extracellular fluid volume is a probable determinant [65]. Though it is assumed that improved left ventricular geometry mitigates the cardiac dysfunction of ESRD, no studies involving SDHD have demonstrated this to date.

Nocturnal home haemodialysis (NHD) is a treatment paradigm whereby patients self-administer their dialysis on 4–6 nights per week with each session lasting between 6 and 8 h. This strategy combines both high frequency treatments with long duration and has well-documented physiological restorative properties [67]. The cardiovascular benefits were among the first recognized advantages of NHD with a reduction in LVMI of 22% observed in ESRD patients after converting to NHD. Conversely, control subjects remaining on a conventional three times weekly haemodialysis demonstrated a 6% progression of LVMI [68]. This may be particularly relevant for patients with CHF and depressed ejection fraction (EF). In fact, EF improved from 28% to 41% in a small cohort of ESRD patients with CHF [69]. The consistent reduction in blood pressure and antihypertensive medication use, as well as the regression of left ventricular mass associated with NHD, was recently confirmed in a randomized controlled trial comparing cardiovascular characteristics between NHD and conventional haemodialysis [70]. Attenuated LVMI likely results from a decrease in total peripheral resistance and mean arterial pressure, possibly mediated by decreased circulating catecholamines and improved flow-mediated vascular responsiveness [71]; diminished extracellular fluid volume was not demonstrated but cannot be ruled out [68]. Certainly, NHD represents a promising novel approach to manage ESRD patients with LVDys.

Conclusions

LVDys is highly prevalent in HD patients and confers a worse prognosis in this already highly co-morbid population. The most commonly used measurement technique, 2D echocardiography, can lead to underestimation of LV function rendering interpretation of the literature problematic. The routine use of modern measurement techniques will hopefully allow for more accurate estimates of prevalence.

Limited evidence exists regarding therapeutic options for management in these patients. The most robust data support the use of beta-blocker therapy; however, there remains a paucity of studies to support the routine use of renin–angiotensin system blockade or ASA. Interventional therapies are potentially underutilized in the HD population due to increased rates of complications and under-referral. ICDs appears to be beneficial as a secondary prevention measure; however, the question of its use in primary prevention remains unknown and their widespread adoption is at present cost prohibitive. The benefit of novel management strategies such as cardiac resynchronization and the use of home nocturnal haemodialysis have shown promise for managing these patients; however, larger trials need to be carried out to confirm original findings in these areas.

In conclusion, much work remains to be done in this high-risk patient group with a significant burden of illness pertaining to LVDys. Large randomized controlled trials are necessary to establish evidence-based guidelines in management of these patients, as therapeutic interventions with demonstrable benefit may not reliably be extrapolated from studies involving LVDys in the non-HD population.

Conflict of interest statement. None declared.

References

1. USRDS. USRDS 2006 Annual Data Report. The National Institute of Health. *Am J Kidney Dis* 2006; 49(Suppl 1): s1
2. Jassal S, Trpeski L, Zhu N *et al*. Changes in survival among elderly patients initiating dialysis from 1990 to 1999. *CMAJ* 2007; 177: 1033–1038
3. Stack AG, Bloembergen WE. A cross-sectional study of the prevalence and clinical correlates of congestive heart failure among incident US dialysis patients. *Am J Kidney Dis* 2001; 38: 992–1000
4. Collins AJ. Impact of congestive heart failure and other cardiac diseases on patient outcomes. *Kidney Int Suppl* 2002; 8: S3–S7.
5. Trespalacios FC, Taylor AJ *et al*. Heart failure as a cause for hospitalization in chronic dialysis patients. *Am J Kidney Dis* 2003; 41: 1267–1277
6. Silberberg JS, Barre PE *et al*. Impact of left ventricular hypertrophy on survival in end-stage renal disease. *Kidney Int* 1989; 36: 286–290
7. Zoccali C, Benedetto FA. Prognostic impact of the indexation of left ventricular mass in patients undergoing dialysis. *J Am Soc Nephrol* 2001; 12: 2768–2774
8. Zoccali C, Benedetto FA *et al*. Prognostic value of echocardiographic indicators of left ventricular systolic function in asymptomatic dialysis patients. *J Am Soc Nephrol* 2004; 15: 1029–1037
9. Foley RN, Parfrey P *et al*. The prognostic importance of left ventricular geometry in uremic cardiomyopathy. *J Am Soc Nephrol* 1995; 5: 2024–2031
10. London GM, Pannier B *et al*. Alterations of left ventricular hypertrophy in and survival of patients receiving hemodialysis: follow-up of an interventional study. *J Am Soc Nephrol* 2001; 12: 2759–2767
11. K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. *Am J Kidney Dis* 2005; 45(Suppl 3): S1–S153.
12. SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991; 325: 293–302
13. Levy D, Savage DD *et al*. Echocardiographic criteria for left ventricular hypertrophy: the Framingham Heart Study. *Am J Cardiol* 1987; 59: 956–960
14. Foley RN, Parfrey PS *et al*. Clinical and echocardiographic disease in patients starting end-stage renal disease therapy. *Kidney Int* 1995; 47: 186–192
15. Foley RN, Parfrey PS *et al*. Long-term evolution of cardiomyopathy in dialysis patients. *Kidney Int* 1998; 54: 1720–1725

16. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis* 1998; 32(Suppl 3): S112–S119
17. Harnett JD, Foley RN *et al*. Congestive heart failure in dialysis patients: prevalence, incidence, prognosis and risk factors. *Kidney Int* 1995; 47: 884–890
18. Parfrey PS, Foley RN *et al*. Outcome and risk factors for left ventricular disorders in chronic uraemia. *Nephrol Dial Transplant* 1996; 11: 1277–1285
19. Mallamaci F, Zoccali C, Tripepi G *et al*. Diagnostic potential of cardiac natriuretic peptides in dialysis patients. *Kidney Int* 2001; 59: 1559–1566
20. Joki N, Hase H *et al*. Combined assessment of cardiac systolic dysfunction and coronary atherosclerosis used to predict future cardiac deaths after starting hemodialysis. *Am J Nephrol* 2003; 23: 458–465
21. Greaves SC, Gamble GD *et al*. Determinants of left ventricular hypertrophy and systolic dysfunction in chronic renal failure. *Am J Kidney Dis* 1994; 24: 768–776
22. Zoccali C, Benedetto FA, Mallamaci F *et al*. Prognostic value of echocardiographic indicators of left ventricular systolic function in asymptomatic dialysis patients. *J Am Soc Nephrol* 2000; 15: 1029–1037
23. Bouchard J, Madore F. Inadequate treatment of congestive heart failure in dialysis patients. *Semin Dial* 2007; 20: 383–386
24. Ritz E, Dikow R *et al*. Congestive heart failure due to systolic dysfunction: the Cinderella of cardiovascular management in dialysis patients. *Semin Dial* 2002; 15: 135–140
25. Levin A, Thompson CR *et al*. Left ventricular mass index increase in early renal disease: impact of decline in hemoglobin. *Am J Kidney Dis* 1999; 34: 125–134
26. Levin A, Lewis M *et al*. Prevalent left ventricular hypertrophy in the predialysis population: identifying opportunities for intervention. *Am J Kidney Dis* 1996; 27: 347–354
27. Portoles J, Torralbo A *et al*. Cardiovascular effects of recombinant human erythropoietin in predialysis patients. *Am J Kidney Dis* 1997; 29: 541–548
28. Kuriyama S, Tomonari H *et al*. Reversal of anemia by erythropoietin therapy retards the progression of chronic renal failure, especially in nondiabetic patients. *Nephron* 1997; 77: 176–185
29. Foley RN, Parfrey PS *et al*. Effect of hemoglobin levels in hemodialysis patients with asymptomatic cardiomyopathy. *Kidney Int* 2000; 58: 1325–1335
30. Besarab A, Bolton WK *et al*. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med* 1998; 339: 584–590
31. Mahadevan G, Davis RC *et al*. Left ventricular ejection fraction: Are the revised cut-off points for defining systolic dysfunction sufficiently evidence based? *Heart* 2008; 94: 426–428
32. Parfrey PS, Collingwood P *et al*. Left ventricular disorders detected by M-mode echocardiography in chronic uraemia. *Nephrol Dial Transplant* 1996; 11: 1328–1331.
33. Kilickap M, Sayin T *et al*. Intravascular volume dependency of left ventricular mass calculation by two-dimensional guided M-mode echocardiography. *Can J Cardiol* 2006; 23: 219–222.
34. Hartnett JD, Collingwood P *et al*. The reliability and validity of echocardiographic measurement of left ventricular mass index in hemodialysis patients. *Nephron* 1993; 65: 3
35. Martin LC, Cornejo IV *et al*. Influence of fluid volume variations on the calculated value of left ventricular mass measured by echocardiogram in patients submitted to hemodialysis. *Ren Fail* 2003; 25: 43–53
36. Stewart GA, Foster J *et al*. Echocardiography overestimates left ventricular mass in hemodialysis patients relative to magnetic resonance imaging. *Kidney Int* 1999; 56: 2248–2253
37. Sugeng L, Weinnert L *et al*. Quantitative assessment of left ventricular size and function–side by side comparison of real-time three dimensional echocardiography and computed tomography with magnetic resonance reference. *Circulation* 2007; 114: 654–661
38. mcIntyre CW, Selby NM *et al*. Hemodialysis-induced cardiac dysfunction is associated with an acute reduction in global and segmental myocardial blood flow. *CJASN* 2007; 3: 19–26
39. Furgeson S, Chonchol M. Beta-blockade in chronic dialysis patients. *Semin Dial* 2008; 21: 43–48
40. Cice G, Di Benedetto A *et al*. Dilated cardiomyopathy in dialysis patients—beneficial effects of carvedilol: a double-blind, placebo-controlled trial. *J Am Coll Cardiol* 2001; 41: 1438–1444
41. Cice G, D'Andrea A *et al*. Cardvedilol increases two year survival in dialysis patients with dilated cardiomyopathy: a prospective, placebo-controlled trail. *J Am Coll Cardiol* 2003; 41: 1438–1444
42. Hayashi A, Kaneshiro M, Takemitsu Y *et al*. Low doses of losartan and trandolapril improve arterial stiffness in hemodialysis patients. *Am J Kidney Dis* 2005; 45: 866–874.
43. Shibasaki Y, Nishiue T *et al*. Angiotensin II type 1 receptor antagonist, losartan, causes regression of left ventricular hypertrophy in end-stage renal disease. *Nephron* 2002; 90: 256–261
44. Suzuki H, Okada H *et al*. A selective angiotensin receptor antagonist, valsartan, produced regression of left ventricular hypertrophy associated with a reduction of arterial stiffness. *Adv Perit Dial* 2003; 19: 59–66
45. Li PK, Wong TY *et al*. Effects of an angiotensin-converting enzyme inhibitor on residual renal function in patients receiving peritoneal dialysis. A randomized, controlled study. *Ann Intern Med* 2003; 139: 105–112
46. Zannad F, Lehert P *et al*. Prevention of cardiovascular events in end-stage renal disease: results of a randomized trial of fosinopril and implications for future studies. *Kidney Int* 2006; 70: 1318–1324
47. Takahashi A, Takase H *et al*. Candesartan, an angiotensin II type-1 receptor blocker, reduces cardiovascular events in patients on chronic haemodialysis—a randomized study. *Nephrol Dial Transplant* 2006; 21: 2507–2512
48. Trespalacios FC, Agodoa LY *et al*. Heart failure as a cause for hospitalization in chronic dialysis patients. *Am J Kidney Dis* 2003; 41: 1267–1277
49. Cleland JG, Jafri S *et al*. The Warfarin/Aspirin Study in Heart Failure (WASH): a randomized trial comparing antithrombotic strategies for patients with heart failure. *Am Heart J* 2004; 148: 157–164
50. USRDS. Atlas of end-stage renal disease in the United States. *USRDS 2006 Annual Data Report*. National Institute of Diabetes and Digestive Kidney Disease 2006
51. Bleyer AJ, Tell GS *et al*. Characteristics of sudden death in hemodialysis patients. *Kidney Int* 2006; 69: 2268–2273
52. ACC/AHA. Guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. *Circulation* 2005; 112: e154–e235
53. Herzog CA, Li S *et al*. Survival of dialysis patients after cardiac arrest and the impact of implantable cardioverter defibrillators. *Kidney Int* 2005; 68: 818–825
54. Abraham WT, FW, Smith AL *et al*. for the MIRACLE Study Group. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002; 346: 1845–1853
55. Bristow MR, Saxon LA *et al*. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004; 350: 2140–2150
56. Saxon LA, Bristow MR *et al*. Predictors of sudden cardiac death and appropriate shock in the comparison of medical therapy, pacing, and defibrillation in heart failure (COMPANION) trial. *Circulation* 2006; 114: 2766–2772
57. Bloom H, Heeke B *et al*. Renal insufficiency and the risk of infection from pacemaker or defibrillator surgery. *Pacing Clin Electrophysiol* 2006; 29: 142–145
58. Dasgupta A, Montalvo J *et al*. Increased complication rates of cardiac rhythm management devices in ESRD patients. *Am J Kidney Dis* 2007; 49: 656–663
59. Stack AG, Molony DA *et al*. Impact of dialysis modality on survival of new ESRD patients with congestive heart failure in the United States. *Kidney Int* 2003; 64: 1071–1079

60. Enia G, Mallamaci F *et al*. Long-term CAPD patients are volume expanded and display more severe left ventricular hypertrophy than haemodialysis patients. *Nephrol Dial Transplant* 2001; 16: 1459–1464
61. Konings CJ, Kooman JP *et al*. Fluid status, blood pressure, and cardiovascular abnormalities in patients on peritoneal dialysis. *Perit Dial Int* 2002; 22: 477–487
62. Koc M, Toprak A *et al*. Uncontrolled hypertension due to volume overload contributes to higher left ventricular mass index in CAPD patients. *Nephrol Dial Transplant* 2002; 17: 1661–1666
63. Konings CJAM, Kooman JP *et al*. Effect of icodextrin on volume status, blood pressure and echocardiographic parameters: a randomized study. *Kidney Int* 2003; 63: 1556–1563
64. Asci G, Ozkahya M *et al*. Volume control associated with better cardiac function in long-term peritoneal dialysis patients. *Perit Dial Int* 2006; 26: 85–88
65. Fagugli R, Reboldi G *et al*. Short daily hemodialysis: blood pressure control and left ventricular mass reduction in hypertensive hemodialysis patients. *Am J Kidney Dis* 2001; 38: 371–376
66. Traeger J, Galland R *et al*. Six years' experience with short daily hemodialysis: Do the early improvements persist in the mid and long term? *Hemodialysis Int* 2004; 8: 151–158
67. Pauly RP, Chan CT. Reversing the risk factor paradox: Is daily nocturnal hemodialysis the solution? *Semin Dial* 2007; 20: 539–543
68. Chan CT, Floras JS *et al*. Regression of left ventricular hypertrophy after conversion to nocturnal hemodialysis. *Kidney Int* 2002; 61: 2235–2239
69. Chan C *et al*. Improvement in ejection fraction by nocturnal haemodialysis in end-stage renal failure patients with coexisting heart failure. *Nephrol Dial Transplant* 2002; 17: 1518–1521
70. Culleton BF *et al*. Effect of frequent nocturnal hemodialysis versus conventional hemodialysis on left ventricular mass and quality of life: a randomized controlled trial. *JAMA* 2007; 298: 1291–1299
71. Chan CT *et al*. Short-term blood pressure, noradrenergic, and vascular effects of nocturnal home hemodialysis. *Hypertension* 2003; 42: 925–931

Received for publication: 16.4.08
Accepted in revised form: 29.5.08