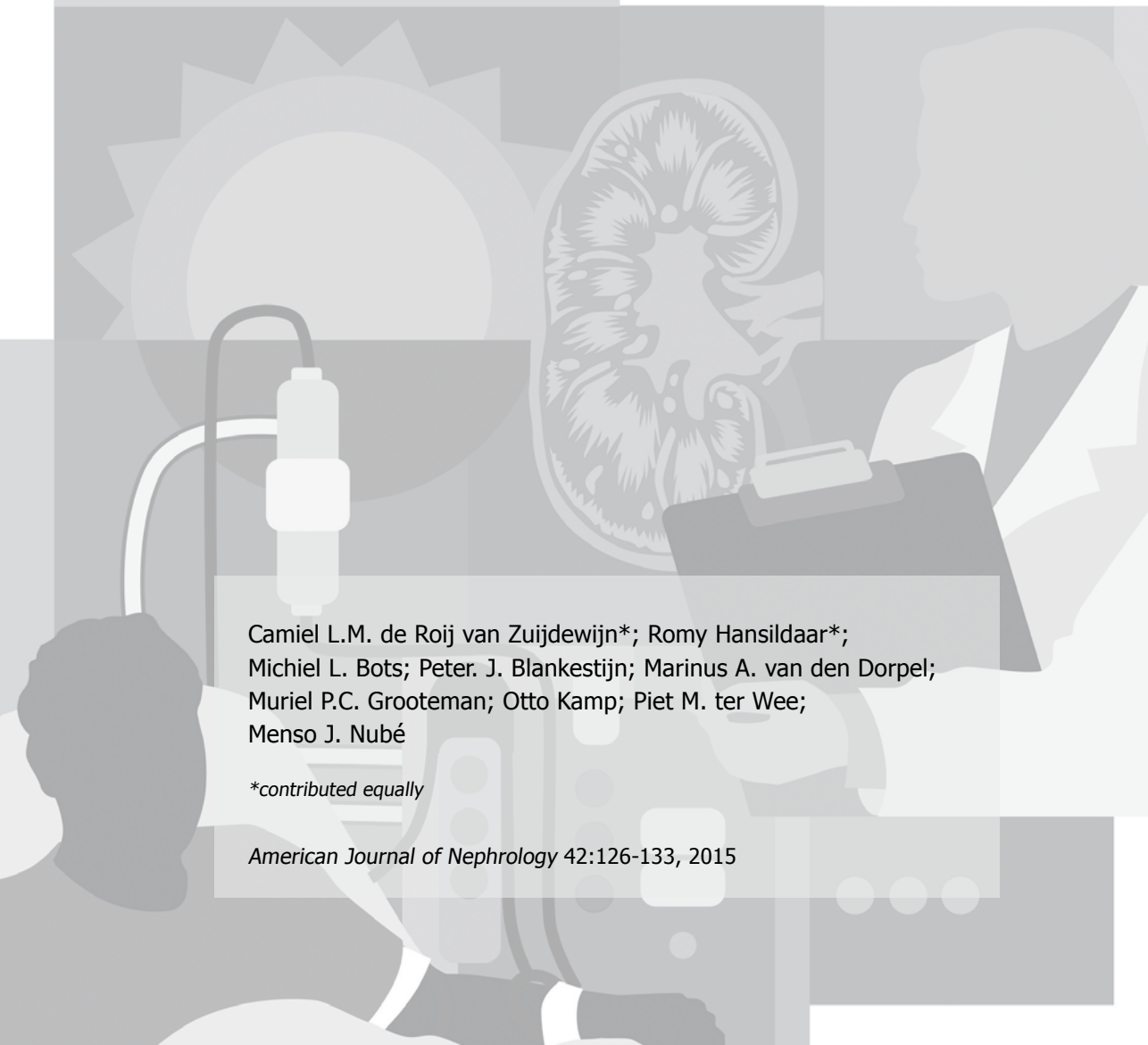
Chapter 3.3

Eccentric left ventricular hypertrophy and sudden death in patients with end-stage kidney disease



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American Journal of Nephrology 42:126-133, 2015

ABSTRACT

Introduction

Both all-cause and cardiovascular mortality risk are extremely high in patients with end-stage kidney disease (ESKD). Sudden death accounts for approximately one-quarter of all fatal events. Left ventricular hypertrophy (LVH) is a known risk factor for mortality and can be divided in two types: concentric and eccentric. This study evaluated possible differences in all-cause mortality, cardiovascular mortality and sudden death between prevalent ESKD patients with concentric and eccentric LVH.

Methods

Participants of the CONvective TRAnsport STudy who underwent transthoracic echocardiography (TTE) at baseline were analyzed. In patients with LVH, a relative wall thickness ≤0.42 was considered eccentric and >0.42 was considered concentric hypertrophy. Cox proportional hazards models, adjusted for potential confounders, were used to calculate hazard ratios (HRs) of patients with eccentric LVH versus patients with concentric LVH for all-cause mortality, cardiovascular mortality and sudden death.

Results

TTE was performed in 328 CONTRAST participants. LVH was present in 233 participants (71%), of which 87 (37%) had concentric LVH and 146 (63%) eccentric LVH. The HR for all-cause mortality of eccentric versus concentric LVH was 1.14 (p=0.52), for cardiovascular mortality 1.79 (p = 0.12) and for sudden death 4.23 (p=0.02) in crude analyses. Propensity score-corrected HR for sudden death in patients with eccentric LVH versus patients with concentric LVH was 5.22 (p=0.03).

Conclusions

(1) The hazard for all-cause mortality, cardiovascular mortality and sudden death is markedly increased in patients with LVH. (2) The sudden death risk is significantly higher in ESKD patients with eccentric LVH compared to subjects with concentric LVH.

INTRODUCTION

The cardiovascular mortality risk in patients with end-stage kidney disease (ESKD) is approximately 10 to 20 times higher than in age- and sex-matched individuals in the general population,[1,2] and has been attributed to various factors, such as the deleterious effects of retained uremic toxins, chronic micro-inflammation, increased sympathetic activity, premature atherosclerosis, fluid overload and hypertension.[3,4] Left ventricular hypertrophy (LVH) is an independent risk factor for an adverse clinical outcome, both in the general population and in dialysis patients.[5-7] At the initiation of hemodialysis (HD), LVH is present in 70% of ESKD patients. Most evidence suggests that LVH does not regress, but aggravates in this patient group over time.[8] From a hemodynamic view, LVH is an adaptive remodeling process, which compensates for the increase in cardiac workload induced by an increased afterload (pressure overload), an increased preload (volume overload), or both.[9] Generally, an increased afterload leads to concentric hypertrophy, while an increased preload leads to the development of eccentric hypertrophy.[10,11] Although there is considerable overlap between these two entities, the first has been related to diastolic dysfunction and the second to systolic dysfunction.[12] Clinically, however, it is often difficult to distinguish these two pathological conditions unambiguously from each other. Sudden cardiac death is common in both peritoneal dialysis and HD patients and accounts for about one-quarter of mortality in this patient group.[13,14] Given this high occurrence rate, identification of risk factors for sudden death, and thus possibly opportunities for preventive interventions, seems highly required. As LVH is a well-established risk factor for all-cause and cardiovascular mortality and particularly for sudden cardiac death,[15] the question arises whether clinical outcome is dissimilar for ESKD patients with different types of LVH, i.e. eccentric or concentric LVH. To address this question, data from the CONvective TRAnsport STudy (CONTRAST) were analyzed.

METHODS

The CONTRAST study (NCT00205556) was designed to investigate the effect of post-dilution online hemodiafiltration (HDF) compared to low-flux HD on all-cause mortality and cardiovascular events. Methods have been described elsewhere.[16,17] In brief, a total of 714 patients were enrolled from June 2004 until December 2009. Adults (≥ 18 years) were eligible if treated with HD 2 or 3 times per week for at least 2 months with a $spKt/V_{urea} \geq 1.2$. Furthermore, patients had to be able to understand the study procedures. Exclusion criteria were treatment with HDF or

high-flux HD in the 6 months preceding randomization, severe incompliance to the dialysis prescription, a life expectancy ≤3 months due to non-renal disease or participation in another clinical intervention trial evaluating cardiovascular outcomes. CONTRAST was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines and approved by a central medical ethics review board. Written informed consent was obtained from all patients prior to enrolment. The present analysis was performed in a subset of 328 participants who underwent transthoracic echocardiography (TTE) at baseline.

Patient characteristics and clinical definitions

At baseline, various demographical, clinical and laboratory data were collected. Previous cardiovascular disease was defined as a history of angina pectoris, myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, transient ischemic attack, cerebrovascular accident, carotid endarterectomy, claudicatio intermittens, percutaneous transluminal angioplasty or bypass of the large leg arteries, amputation, vascular intervention of the aorta or percutaneous transluminal angioplasty of the renal arteries. Systolic and diastolic blood pressures were measured before and after three consecutive dialysis sessions at baseline using a standard electronic sphygmomanometer and averaged for analysis. Interdialytic weight gain (IDWG) was calculated as the mean net ultrafiltration of three consecutive dialysis sessions at baseline. Relative IDWG was defined as the percentage of IDWG relative to dry weight, which was determined as the mean of three consecutive post-dialysis body weight measurements. Body mass index (BMI) was computed as the quotient of weight (kg) divided by height (m) squared. Smoking habit was determined as either active, former or never smoker. Urine volumes were determined using 24 hour urine collection at baseline.

Sudden death was defined as either certain sudden death (death within 1 hour after onset of symptoms as verified by a witness) or probable sudden death (death within 24 hours after onset of symptoms as verified by a witness or found dead by a witness). An independent endpoint adjudication committee of physicians reviewed source documentation for all events, including sudden death. Follow-up of patients was complete as subjects remained enclosed after discontinuation of the randomized treatment due to renal transplantation, switch to peritoneal dialysis, move to another non-participating center or other reasons.

Echocardiography

As participating dialysis centres were located in both university and community based hospitals, TTE was only performed in specialized centres (15 out of 29

facilities). Measurements were performed according to the standard American Society of Echocardiography protocols [18] on a mid-week non-dialysis day by an echocardiographer at the participating local hospital. From the parasternal long axis position, the left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), posterior wall thickness (PWT) and septal wall thickness were determined. Afterwards, the ultrasound investigations were assessed by an independent experienced echocardiographer at the core laboratory (O.K., VU University Medical Center, Amsterdam, the Netherlands), who was blinded for other patient data. Left ventricular mass (LVM) was calculated using the formula of Devereux and Reickek[19] and modified in accordance with the recommendations of the American Society of Echocardiography.[18] LVH was defined as LVM/height^2.7 >44 g/m^2.7 for women and >48 g/m^2.7 for men.[20] Relative wall thickness (RWT) was calculated by the following formula: RWT = [(2*PWT)/LVEDD]. This formula permits categorization of normal geometry (RWT ≤ 0.42) or concentric remodeling (RWT > 0.42) for those with a LVM in the normal range. Patients with an increased LVM have either eccentric (RWT ≤ 0.42) or concentric (RWT > 0.42) LVH.[20,21] This partition value is in accordance with the current standard American Society of Echocardiography guidelines,[20] and based on a study of Ganau *et al*.[22] Left ventricular ejection fraction (LVEF) was automatically computed by the echocardiography software according to the Teicholz method. Lastly, peak systolic left ventricular wall stress (PSLVWS) was calculated by the formula from Wilson et al: PSLVWS (*10^3 dynes/cm^2) = 0.86*(0.334*SBP*LVEDD)/(PWT*(1+(PWT/LVEDD)))-2.[23]

Statistical analysis

Kaplan-Meier curves were plotted for all-cause mortality, cardiovascular mortality and sudden death for the four LV geometry groups. Using Cox proportional hazards models, hazard ratios (HRs) were calculated for all-cause mortality, cardiovascular mortality and sudden death for patients with LVH versus patients without LVH. Within the LVH group, HRs were determined for patients with eccentric LVH versus patients with concentric LVH for all-cause mortality, cardiovascular mortality and sudden death, again using Cox proportional hazards models. Due to a limited number of sudden deaths, adjusting for all potential confounders would lead to an overfitted and thus unstable statistical model. Therefore, propensity scores were calculated using logistic regression models including the following upfront determined variables, which were considered potential confounders: age, history of cardiovascular disease, smoking status, diabetes mellitus, previous kidney transplantation, residual kidney function, dialysis vintage, haemoglobin level, serum albumin, mean pre-dialysis systolic blood pressure, dialysis modality, dry weight, relative IDWG, use of calcium containing phosphate binders, use of beta-blockers

and the use of a RAS inhibitor. Two propensity score models were fitted: one for the propensity to develop LVH and one for the propensity to develop eccentric or concentric LVH. All confounders were determined at baseline. The proportional hazards assumption of the Cox regression models was checked with log minus log plots and was not violated. A two-sided $p<0.05$ was considered statistically significant. All statistical analyses were performed using SPSS software version 20.0 (SPSS Inc. Headquarters, Chicago, Illinois, US).

RESULTS

Patients

Out of the 714 patients included in CONTRAST, 328 individuals underwent TTE at baseline and were thus available for analysis. Baseline patient characteristics of the investigated (TTE) cohort and baseline characteristics of patients stratified by LVH type (i.e. concentric or eccentric LVH) are presented in table 1. Of all investigated patients, mean age was 63.1 years and 61% were male. Diabetes mellitus was present in 25.6% and 146 patients (44.5%) had a history of cardiovascular disease. Median dialysis vintage was 2.0 years. Apart from a significantly lower urine output in patients with eccentric LVH (median 478 mL versus 519 mL/24h in patients with concentric LVH; p <0.05), there were no marked differences between the two groups. Baseline characteristics of the entire CONTRAST cohort and the investigated participants are shown in supplementary table 1. Marked differences were not observed.

Echocardiography

Subdividing patients by the left ventricular geometric pattern indexed for height$^{2.7}$ results in the distribution as shown in figure 1. Thus, out of the 328 patients, 233 (71%) had LVH at baseline. In this group, 37% had concentric LVH and 63% had eccentric LVH. Results of the TTE measurements are shown in supplementary table 2 for all investigated patients and stratified by LVH type. While the ejection fraction was markedly lower in patients with eccentric LVH as compared to patients with concentric LVH (p < 0.01), peak systolic left ventricular wall stress was considerably higher in patients with eccentric LVH (median 211*10^3 dynes/cm^2) than in patients with concentric LVH (median 130*10^3 dynes/cm^2; p < 0.0005).

During follow-up

During follow up (median 2.98 years, range 0.07-6.53 years), 130 patients (40%) died. Of these patients, 43 (33%) died due to cardiovascular disease. Sudden

Table 1. Baseline patient characteristics

	Echo cor cohort (n=328)	Concentric LVH patients (n=87)	Eccentric LVH patients (n=146)
Demographic parameters			
Sex (male)	201 (61.3%)	53 (60.9%)	87 (59.6%)
Age (years)	63.1 (13.3)	62.5 (13.1)	65.2 (12.8)
Height (cm)	168.5 (10.8)	166.9 (10.7)	166.5 (10.4)
Dry weight (kg)	72.1 (14.3)	72.4 (13.2)	71.7 (14.4)
BMI (kg/ m²)	25.4 (4.9)	26.2 (5.2)	25.9 (5.0)
Dialysis properties			
Duration of dialysis (hours)	3.76 (0.38)	3.83 (0.33)	3.71 (0.39)
Blood flow rate (mL/min)	296 (39)	293 (41)	292 (39)
Vascular access (AV fistula)	261 (79.6%)	73 (83.9%)	114 (78.1%)
Relative IDWG (%)	2.74 (1.93–3.52)	2.90 (2.05–3.62)	2.70 (1.89–3.43)
Medical history			
Cardiovascular disease	146 (44.5%)	35 (40.2%)	77 (52.7%)
Diabetes	84 (25.6%)	21 (24.1%)	44 (30.1%)
Previous kidney transplant	30 (9.1%)	4 (4.6%)	11 (7.5%)
Residual kidney function*	171 (52.1%)	49 (56.3%)	79 (54.1%)
if yes, volume (mL)	561 (300-1076)	519 (245-873)	478 (388-1126)
Dialysis vintage (years)	2.0 (1.0–4.0)	1.83 (1.0–3.25)	1.88 (0.92–3.69)
Medication			
Diuretic	128 (39.0%)	35 (40.2%)	64 (43.8%)
Alpha blocker	22 (6.7%)	9 (10.3%)	8 (5.5%)
Beta blocker	176 (53.7%)	59 (67.8%)	80 (54.8%)
RAS inhibitor	163 (49.7%)	53 (60.9%)	77 (52.7%)
Calcium antagonist	106 (32.3%)	33 (37.9%)	49 (33.6%)
Lipid lowering therapy	152 (46.3%)	47 (54.0%)	71 (48.6%)
Platelet aggregation inhibitor	115 (35.1%)	27 (31.0%)	58 (39.7%)
Biochemical parameters			
Hemoglobin (g/L)	7.30 (0.78)	7.40 (0.81)	7.22 (0.75)
Phosphate (mmol/L)	1.67 (0.50)	1.70 (0.55)	1.66 (0.50)
Albumin (g/L)	40.6 (4.0)	40.1 (3.6)	40.4 (4.1)
Creatinin (µmol/L)	883 (252)	880 (243)	839 (221)
Cholesterol (mmol/L)	3.69 (1.01)	3.57 (0.90)	3.65 (1.04)
Hemodynamic measurements			
Mean SBP (mmHg)	148 (21)	150 (21)	151 (22)
Mean DBP (mmHg)	77 (12)	77 (11)	76 (12)

Data are reported as mean (standard deviation [SD]), median (interquartile range [IQR]) or number (percentage), when appropriate.

* defined as diuresis > 100mL/24h

Abbreviations: LVH = left ventricular hypertrophy, BMI = Body Mass Index, RAS = renin-angiotensin system, AV = arteriovenous, IDWG = interdialytic weight gain, SBP = systolic blood pressure, DBP = diastolic blood pressure

death occurred in 24 patients (18% of all deaths) and was therefore responsible for over half (56%) of cardiovascular mortality. As can be seen in supplementary table 3, patients with LVH had a borderline significant higher risk for all-cause mortality (adjusted HR 1.60; 95% CI 0.96-2.66; *p*=0.07) and a significantly higher risk for cardiovascular mortality (adjusted HR 3.49; 95% CI 1.11-10.95; *p*=0.03), which was exceptionally increased in the case of sudden death (adjusted HR 14.10; 95% CI 1.72-115.35; *p*=0.01).

Results of the subdivision of the left ventricle in geometric patterns are represented in table 2, figure 2 and supplementary figures 1 and 2. Differences between eccentric and concentric LVH were not observed for all-cause and cardiovascular mortality (adjusted HRs 0.87 and 1.49; *p*-values 0.57 and 0.36, respectively). However, the risk for sudden death was significantly increased in subjects with eccentric LVH (adjusted HR 5.22; 95% CI 1.14-23.94, *p*=0.03 and unadjusted log-rank test *p*=0.01).

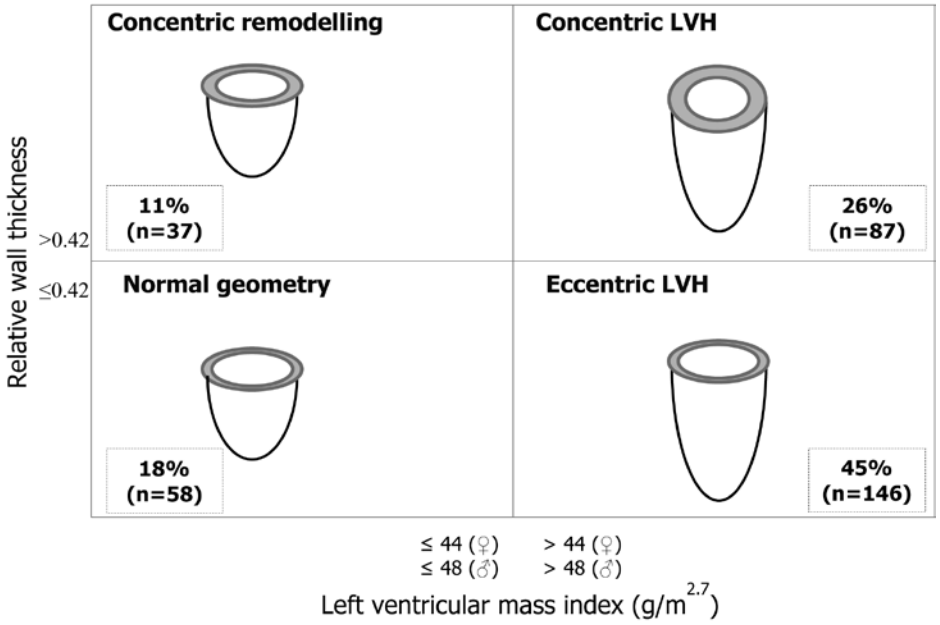


Figure 1. Distribution of left ventricular geometric patterns at baseline. As can be seen from this figure, a total of 231 patients had LVH (71%). Out of these 87 (37%) were classified as concentric LVH and 146 (63%) as eccentric LVH.

Table 2. Hazard ratios for adverse events in patients with eccentric LVH versus concentric LVH.

	No. of events	Person years	HR	95% CI	*p*-value HR
Crude					
All-cause mortality	101	717	1.14	0.76-1.72	0.52
Cardiovascular mortality	38	717	1.79	0.87-3.68	0.12
Sudden death	23	717	4.23	1.26-14.25	0.02
*Adjusted**					
All-cause mortality	81	669	0.87	0.54-1.40	0.57
Cardiovascular mortality	28	669	1.49	0.63-3.54	0.36
Sudden death	17	669	5.22	1.14-23.94	0.03

*Adjusted with a propensity score including the variables: age, history of cardiovascular disease, diabetes mellitus, smoking status, previous kidney transplantation, residual kidney function, dialysis vintage, relative interdialytic weight gain, serum albumin, haemoglobin, mean pre-dialysis systolic pressure, dialysis modality, post dialysis baseline weight, use of calcium containing phosphate binders and RAS inhibitors.

Abbreviations: HR = hazard ratio, CI = confidence interval, LVH = left ventricular hypertrophy.

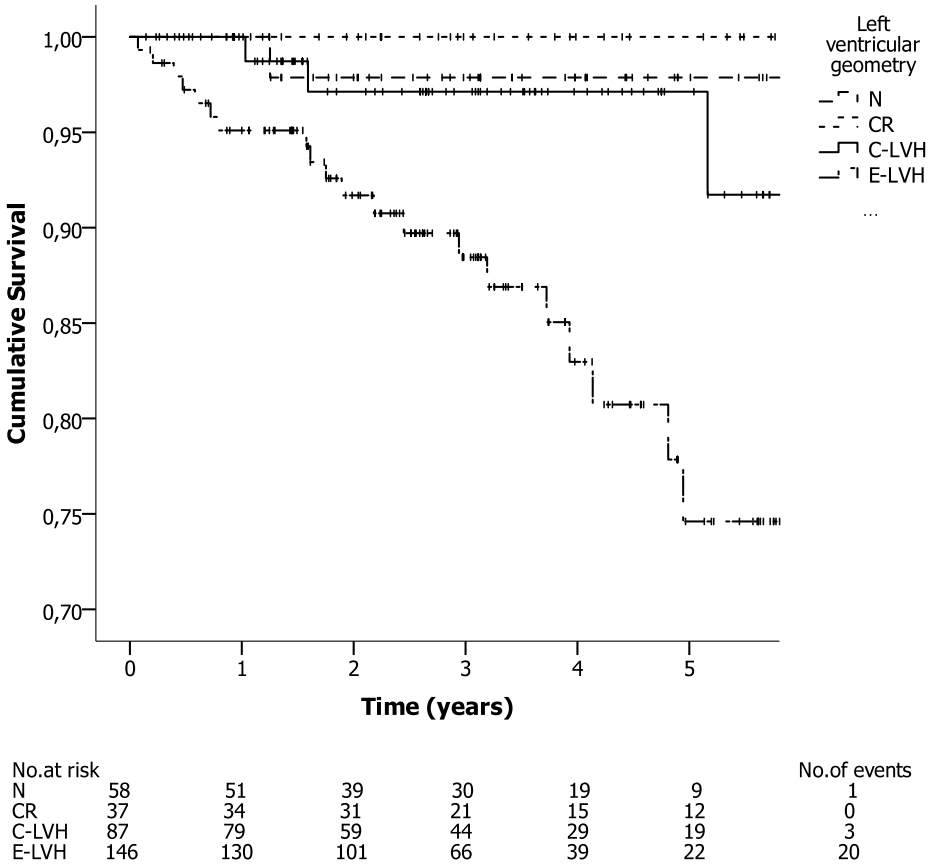


Figure 2. Unadjusted survival curves for left ventricular geometric patterns for sudden death: normal (N), concentric remodeling (CR), concentric LVH (C-LVH) and eccentric LVH (E-LVH).

DISCUSSION

Previously, we showed that patients with a high LVM are at increased risk for all-cause mortality, cardiovascular mortality and sudden death.[15] These findings were confirmed in the present investigation. Above and beyond, we investigated the geometric subdivision in this patient group. From this analysis it appeared that patients with eccentric LVH have a fivefold increased risk of sudden death, if compared to those with concentric LVH. To our knowledge, this is the first study in patients with ESKD relating sudden death to the type of LVH. As sudden death accounts for a quarter of all deaths and about half of cardiovascular mortality in this patient group, our findings may have important clinical consequences.

LVM can be indexed for height$^{2.7}$ or for BSA.[7,24] In the present analysis, LVM was indexed for height$^{2.7}$, as this method is independent of body weight, which is critically influenced by malnutrition and fluid status in this patient group.[21] LVH is associated with sudden death in both non-renal[25] and renal patients.[26] As shown by meta-analysis, regression of LVH during antihypertensive treatment was associated with a marked reduction in the risk of a cardiovascular event.[27] Unfortunately, however, in the vast majority of dialysis patients, LVH deteriorates over time.[8,25,27]

While concentric LVH has been shown to predominate in pre-dialysis patients,[28,29] we found that eccentric LVH is approximately twice as prevalent as concentric LVH in subjects undergoing dialysis. Moreover, in our study, eccentric LVH was far more often associated with sudden death than concentric LVH (HR 5.22 after correction). As for the prevalence of eccentric LVH, comparable findings were previously published by Paoletti *et al* in 42 dialysis patients with LVH who suffered from 30 fatal and non-fatal cardiovascular events.[30] Since eccentric LVH results particularly from volume expansion in ESKD,[10,11] as suggested in our study by a slight, but significantly lower urinary output than individuals with concentric LVH and an extremely high peak systolic left ventricular wall stress, stringent fluid control may help to reduce mortality.

Considering clinical outcomes, the results of the Paoletti study and our analysis seem largely complementary. In our study sudden death predominated in the eccentric type and all-cause mortality did not differ, whereas in the Paoletti study, the incidence of fatal and non-fatal cardiovascular events was considerably higher in patients with the eccentric type. Thus, regardless of the dissimilarities in patient number, length of follow-up, patient selection and classification of events, both studies show a poor outcome for patients with eccentric LVH.[30] Of note, almost

two decades ago, a 17-fold increased risk of mortality in individuals with a dilated cardiac hypertrophy as compared to patients with non-dilated non-hypertrophic hearts was already described in a cohort of 433 chronic HD patients followed for 10 years.[31] Unfortunately, in that study, no data are provided on the causes of death.

The reason for the eccentric type of LVH being especially associated with sudden death in ESKD patients is not clear from the present study. In recent years, a close relationship was recognized between chronic kidney disease (CKD) and cardiovascular abnormalities, which has been termed 'cardiorenal syndrome'. Apart from chronic activation of the sympathetic and renin-angiotensin-aldosteron system,[32] which may lead to sodium and fluid retention and myocardial fibrosis,[33] other risk factors seem to play a role as well. Traditional risk factors, however, such as hypercholesterolemia, hypertension and obesity cannot fully explain the poor clinical outcome in this patient group.[11] Therefore, non-traditional risk factors, including inflammation, oxidative stress, endothelial dysfunction and abnormalities in CKD mineral-bone disease have been implicated in the development of LVH, heart failure and death.[34] Of interest, elevated concentrations of fibroblast growth factor 23 (FGF23), as observed in advanced CKD,[35,36] may link the deteriorating kidney function via derangements in mineral metabolism with the development of LVH.[37] On the tissue level, structural changes of the left ventricle likely play an important role in this respect.[38] Both fibrosis and capillary rarefaction are risk factors for electric instability of the myocardium, favouring local delay in the spread of the action potential leading to complex and sometimes fatal arrhythmias.[38,39] Whether these changes are more pronounced in eccentric LVH than in the concentric type, is a matter for future research. In clinical practice, especially patients with eccentric LVH may benefit from the prophylactic implantation of an implantable cardioverter defibrillator (ICD).

Our study has both limitations and strengths. The most important limitation is that causality cannot be established from this *post hoc* analysis in a subset of CONTRAST patients (n=328) with only a relatively small number of sudden deaths. Second, as TTE was measured in specialized centers only, selection bias may be an issue. However, as the baseline characteristics of this group and the entire CONTRAST cohort (n=714) were similar and the performance of TTE depended on local feasibility of this measurement (and not on patient characteristics), bias by selection seems highly unlikely. Third, as the underlying causes of sudden death are unknown, on theoretical grounds it is conceivable that non-cardiac causes are included as well in our study. In this respect it should be mentioned, however, that from two studies of unexpected deaths on whom autopsy was performed, one large cohort (n=650)[40]

and one smaller cohort of HD patients (n=15),[41] it appeared that 93% of sudden deaths could be attributed to a cardiac origin. Fourth, information on potentially relevant factors, such as time-averaged potassium levels, was not available and could hence not be incorporated in the propensity score model. Lastly, testing three hypotheses in one analysis increases the chance of a coincidental finding. As such, a *p*-value of 0.03 is only borderline significant. Nevertheless, given the magnitude of the association between eccentric LVH and sudden death and the potential for intervention, this finding deserves further investigation. Important strengths of this study are the large sample size, the concise and prospective data collection, the independent review of source documentation for all primary and secondary outcomes and the independent analyses of the echocardiography recordings.

In conclusion, our study confirmed the elevated risk of all-cause mortality, cardiovascular mortality and sudden death in ESKD patients with LVH, if compared to subjects with normal LVM. In addition, from this study it appeared that the eccentric type is approximately twice as prevalent as concentric LVH. Most importantly, however, we found that the risk of sudden death is fivefold greater in patients with eccentric LVH than in subjects with concentric LVH. The clinical implications of this finding, such as the potential to reduce the incidence of fatal arrhythmias in this particular patient group by prophylactic implementation of an ICD, warrant further research. Other topics for future investigations include the search for determinants of LVH type and geometric changes over time.

SUPPLEMENTARY TABLES AND FIGURES

Supplementary table 1. Baseline patient characteristics of the total cohort and the echocardiography cohort.

	Total cohort *(n=714)*	Echocardiography cohort *(n=328)*
Demographic parameters		
Sex (male)	445 (62%)	201 (61%)
Age (years)	64.1 ± 13.7	63.1 ±13.3
Height (cm)	169 ± 10	169 ±11
Weight (kg)	72.4 ± 14.4	72.1 ±14.3
BMI (kg/ m²)	25.4 ± 4.8	25.4 ± 4.9
Dialysis properties		
Duration of dialysis (hours)	3.77 ± 0.38	3.76 ± 0.38
Blood flow rate (mL/min)	300 (280-325)	300 (260-325)
Vascular access (arteriovenous fistula)	567 (80%)	261 (80%)
Medical history		
Cardiovascular disease	313 (44%)	146 (45%)
Diabetes	170(25%)	84 (25%)
Previous kidney transplant	78 (11%)	30 (9%)
Residual kidney function*	376 (53%)	171 (52%)
if yes, volume (mL)	646 (350-1150)	561 (300-1076)
Dialysis vintage (years)	2.0 (1.0-4.0)	2.0 (1.0-4.0)
Medication		
Diuretic	259 (37%)	128 (39%)
Alpha blocker	52 (7%)	22 (7%)
Beta blocker	381 (54%)	176 (54%)
RAS inhibitor	351 (49%)	163 (50%)
Calcium antagonist	230 (32%)	106 (32%)
Lipid lowering therapy	369 (52%)	152 (46%)
Platelet aggregation inhibitor	240 (34%)	115 (35%)
Biochemical parameters		
Hemoglobin (g/L)	118 ± 13	118 ± 13
Phosphate (mmol/L)	1.64 ± 0.49	1.67 ± 0.50
Albumin (g/L)	40.4 ± 3.8	40.6 ± 4.0
Creatinine, pre-dialysis (µmol/L)	861 ± 255	883 ± 252
Cholesterol (mmol/L)	3.68 ± 0.96	3.69 ± 1.01
Hemodynamic measurements		
Mean pre-dialysis systolic pressure (mmHg)	148 ± 22	148 ±21
Mean pre-dialysis diastolic pressure (mmHg)	76 ± 12	77 ± 12

Data are reported as mean (standard deviation [SD]), median (interquartile range [IQR]) or number (percentage), when appropriate.
* defined as diuresis > 100mL/24h
Abbreviations: BMI = Body Mass Index, RAS = renin-angiotensin system

Supplementary table 2. Baseline echocardiographic measurements for all patients and stratified by LVH type (eccentric LVH and concentric LVH).

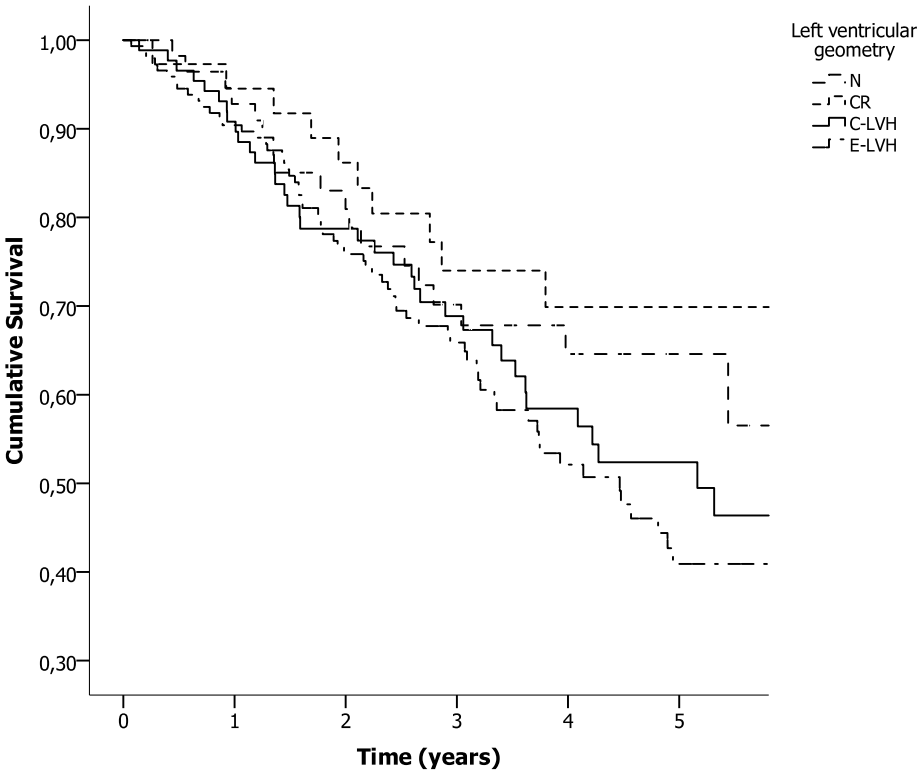
Echocardiographical parameter	Echocardiography cohort *(n =328)*	Concentric hypertrophy *(n =87)*	Eccentric hypertrophy *(n =146)*
RWT = (2*PWTd/LVEDD)[#]	0.39 (0.34-0.47)	0.50 (0.46-0.58)	0.35 (0.31-0.38)
PWTd (mm)[#]	10 (9-11)	12 (11-13)	9 (9-10)
LVEDD (mm)[#]	50 ± 8	47 ± 5	56 ± 6
LVESD (mm)[#]	33 ± 8	30 ± 6	38 ± 8
LVM (g)	227 (183-279)	251 (220-323)	254 (213-299)
LVMi = LVM/height^$^{2.7}$ (g)	58.4 (19.5)	68.7 (18.7)	65.9 (14.8)
LVEF (%)[#]	65 (55-72)	66 (57-72)	61 (52-69)
PSLVWS (*10^^{3} dynex/cm^^{2})[#]	176 (138-214)	130 (110-153)	211 (182-242)
LVH (LVM/height^$^{2.7}$)	233 (71%)	87 (100%)	146 (100%)

Data are reported as mean (SD), median (IQR) or number (percentage), when appropriate.
Abbreviations: LVEDD = left ventricular end-diastolic diameter, LVESD = left ventricular end systolic diameter, PWTd = posterior wall thickness in diastole, RWT = relative wall thickness, LVM = left ventricular mass, LVMi = indexed left ventricular mass, LVEF = left ventricular ejection fraction, PSLVWS = peak systolic left ventricular wall stress, LVH = left ventricular hypertrophy
[#] indicates a significant difference between patients with concentric LVH and eccentric LVH at the level of $p<0.01$

Supplementary table 3. Hazard ratios (HRs) of adverse events for LVH versus non-LVH patients.

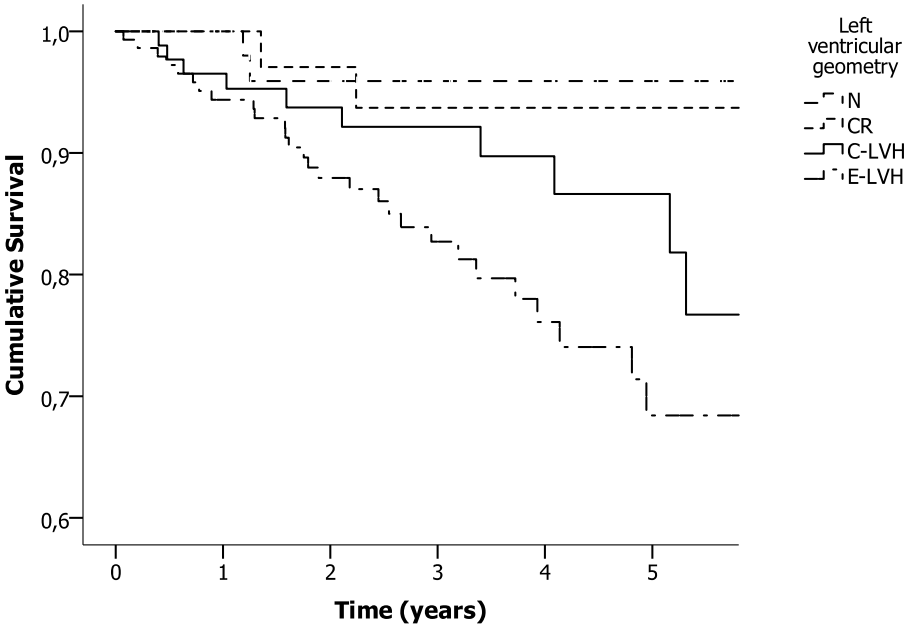
	No. of events	Person years	HR	95% CI	*p*-value HR
Crude					
All-cause mortality	130	1030.75	1.53	1.01-2.31	0.04
Cardiovascular mortality	43	1030.75	3.34	1.31-8.49	0.01
Sudden death	24	1030.75	10.18	1.37-75.37	0.02
*Adjusted**					
All-cause mortality	124	989.68	1.60	0.96-2.66	0.07
Cardiovascular mortality	41	989.68	3.49	1.11-10.95	0.03
Sudden death	23	989.68	14.10	1.72-115.35	0.01

*Adjusted with a propensity score including the variables: age, history of cardiovascular disease, diabetes mellitus, smoking status, previous kidney transplantation, residual kidney function, dialysis vintage, relative interdialytic weight gain, serum albumin, haemoglobin, mean pre-dialysis systolic pressure, dialysis modality, post dialysis baseline weight, use of calcium containing phosphate binders and RAS inhibitors.
Abbreviations: HR = hazard ratios, CI = confidence interval, NA = not applicable, LVH = left ventricular hypertrophy



No. at risk							No. of events
N	58	50	39	30	19	9	19
CR	37	34	31	21	16	12	10
C-LVH	87	79	59	44	29	19	36
E-LVH	146	130	101	66	39	22	65

Supplementary figure 1. Unadjusted survival curves for left ventricular geometric patterns for all-cause mortality: normal (N), concentric remodeling (CR), concentric LVH (C-LVH) and eccentric LVH (E-LVH).



No.at risk							No.of events
N	58	51	39	30	29	9	3
CR	37	34	31	21	15	12	2
C-LVH	87	79	59	44	29	19	9
E-LVH	146	130	101	67	40	22	28

Supplementary figure 2. Unadjusted survival curves for left ventricular geometric patterns for cardiovascular mortality: normal (N), concentric remodeling (CR), concentric LVH (C-LVH) and eccentric LVH (E-LVH).

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