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Left ventricular mass monitoring in the follow-up of dialysis patients: Prognostic value of left ventricular hypertrophy progression

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Background. Regression of left ventricular hypertrophy (LVH) in the setting of a well-planned intervention study has been associated with longer survival in hemodialysis patients. Whether changes in left ventricular mass (LVM) in clinical practice predict survival and cardiovascular events in these patients is still unknown.

Methods. In a prospective study in 161 hemodialysis patients we tested the prognostic value of changes in LVM on survival and incident cardiovascular events. Echocardiography was performed twice, 18 ± 2 SD months apart. Changes in LVM occurring between the first and the second echocardiographic study were then used to predict mortality and cardiovascular events during the ensuing 29 ± 13 months. The prognostic value of LVM changes was tested in a multivariate Cox's model with LVM index (LVMI) (expressed as LVM/height$^{2.71}$), included as a covariate to control for regression to the mean.

Results. The rate of increase of LVMI was significantly ($P = 0.029$) higher in patients with incident cardiovascular events than in those without such events. Accordingly, cardiovascular event-free survival in patients with changes in LVMI below the 25th percentile was significantly ($P = 0.004$) higher than in those with changes above the 75th percentile. In a multiple Cox regression analysis, including age, diabetes, smoking, homocysteine, 1 g/m$^{2.7}$/month increase in LVMI was associated with a 62% increase in the incident risk of fatal and nonfatal cardiovascular events [hazard ratio 1.62 (95% CI 1.13–2.33), $P = 0.009$].

Conclusion. Changes in LVMI have an independent prognostic value for cardiovascular events and provide scientific support to the use of repeated echocardiographic studies for monitoring cardiovascular risk in dialysis patients.

Key words: cardiovascular risk, dialysis, left ventricular hypertrophy and survival.

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There is now consistent evidence that left ventricular hypertrophy (LVH) has an important prognostic value in patients with end-stage renal disease (ESRD) [1–4]. LVH in ESRD is a disorder of multifactorial origin [5] and hypertension, anemia, hyperparathyroidism, chronic volume expansion, and emerging risk factors like inflammation [6, 7], hyperhomocysteinemia [8], high sympathetic activity [9] and accumulation of the endogenous inhibitor of nitric oxide synthase (NOS) asymmetrical dimethylarginine (ADMA) [10] have been implicated in this alteration. Although the mechanisms responsible for the strong link between high left ventricular mass (LVM) and cardiovascular complications are still incompletely understood, LVM is generally considered as an integrator of the long-term effects of several risk factors [11]. Serial echocardiographic studies by Foley et al [12] demonstrated that cardiac enlargement is not halted by the institution of dialysis treatment. This important observation suggests that repeated echocardiographic recordings may provide additional prognostic information in dialysis patients. However, the prognostic value of LVM in ESRD has been examined almost exclusively in follow up studies (i.e., by relating a single LVM measurement made at the start of the study with mortality and incident cardiovascular events [1–3]). The possibility that serial measurements of LVM may give important prognostic information is supported by a multifactorial intervention study by London et al [4] showing that intensive treatment of risk factors for LVH produces a clear regression in LVM index (LVMI) and reduces all-cause and cardiovascular mortality. On the other hand, in the general population worsening of LVH measured by

Table 1. Demographic, somatometric, clinical, biochemical, and echocardiographic data of patients in the original study cohort and in those who repeated the echocardiographic study

	Original cohort ($N = 203$)	Patients who repeated echocardiography ($N = 161$)		P value (second vs. first visit)
		First visit	Second visit	
Age *years*	58.9 ± 14.9	58.0 ± 15.1	60.3 ± 15.0	<0.001
Males *number*	113 (56%)	90 (56%)	90 (56%)	1.00
Body mass index kg/m^2	24.5 ± 4.4	24.4 ± 4.3	24.4 ± 4.2	0.76
Diabetics *number*	28 (14%)	18 (11%)	18 (11%)	1.00
Smokers *number*	78 (38%)	57 (35%)	57 (35%)	1.00
Patients on antihypertensive therapy *number*	78 (38%)	59 (37%)	55 (34%)	0.73
Systolic blood pressure *mm Hg*	140.4 ± 24.8	138.4 ± 24.8	135.9 ± 26.4	0.11
Diastolic biood pressure *mm Hg*	76.3 ± 13.2	76.1 ± 13.7	74.9 ± 13.4	0.21
Heart rate *beats/min*	78.6 ± 10.4	78.6 ± 9.9	79.9 ± 10.9	0.12
Hemoglobin *g/dL*	10.6 ± 1.9	10.5 ± 1.8	11.0 ± 1.6	0.002
Albumin *g/dL*	4.2 ± 0.5	4.2 ± 0.5	3.6 ± 0.5	<0.001
Cholesterol *mg/dL*	206.9 ± 56.1	203.0 ± 55.0	175.4 ± 46.4	<0.001
Calcium × Phosphate mmo^2/L^2	4.54 ± 1.16	4.54 ± 1.20	4.29 ± 1.18	0.01
C-reactive protein *mg/L*	7.7 (3.4–16.3)	7.4 (3.4–16.1)	NA	—
Homocysteine *μmol/L*	26.4 (19.4–42.3)	24.7 (18.3–40.7)	NA	—
ADMA *μmol/L*	2.61 (1.58–3.96)	2.44 (1.56–3.72)	NA	—
Noradrenaline *pmol/L*	3.12 (1.76–5.67)	3.13 (1.70–5.62)	NA	—
Kt/V	1.22 ± 0.27	1.23 ± 0.27	1.32 ± 0.25	<0.001
Left ventricular end diastolic diameter *cm*	5.04 ± 0.66	5.05 ± 0.66	5.14 ± 0.64	0.001
Mean wall thickness *cm*	1.14 ± 0.20	1.11 ± 0.19	1.14 ± 0.16	<0.001
Relative wall thickness	0.44 ± 0.11	0.43 ± 0.10	0.43 ± 0.08	0.68
Left ventricular ejection fraction *%*	58.8 ± 9.8	58.9 ± 10.0	58.0 ± 10.0	0.29
Left ventricular mass index $g/m^{2.7}$	61.0 ± 18.7	59.2 ± 18.1	63.2 ± 19.3	<0.001

ADMA is asymmetrical dimethylarginine; NA is not available.
Data are mean ± SD, median (interquartile range) or percent frequency. Comparisons between groups were made by paired *t* test or chi-squared test, as appropriate.

electrocardiography [13] is associated with a higher risk of cardiovascular events. Likewise, in patients with essential hypertension, persistence or worsening of echocardiographic LVH is associated with a higher risk for subsequent cardiovascular events [14]. Whether LVH progression has a prognostic value in clinical practice in ESRD (i.e., in a context different from that of a well-planned intervention study aimed at reducing LVM) is still undefined. The issue is of relevance because LVH is now regarded as a valid surrogate end point to be targeted in intervention studies in dialysis patients [15]. The purpose of the present study was to determine the prognostic significance of serial measurements of LVM in hemodialysis patients who attended the baseline and follow up echocardiographic measurements in the Cardiovascular Risk Extended Evaluation in Dialysis (CREED) study patients. To this aim we related changes in LVM to all-cause mortality and incident cardiovascular events and tested whether these relationships are independent of baseline LVM, previous cardiovascular events, and of a series of traditional and nontraditional risk factors.

METHODS

Protocol

The protocol was in conformity to the ethical guidelines of our institutions and informed consent was obtained from each participant. All studies were performed during a nondialysis day, between 8:00 a.m. and 1:00 p.m.

Original study cohort

The original hemodialysis cohort was formed by 231 patients (127 males and 104 females). These patients had been on regular dialysis treatment for at least 6 months (median duration 41 months, interquartile range 21 to 106 months). The enrollment criteria in the CREED cohort were no history of congestive heart failure (defined as dyspnea in addition to two of the following conditions: raised jugular pressure, bibasilar crackles, pulmonary venous hypertension or interstitial edema on chest x ray, requiring hospitalization or extra ultrafiltration [16], ejection fraction >35%, and no intercurrent or terminal illnesses. Twenty-eight patients were excluded because of low quality echocardiographic recordings. Thus, 203 patients (113 males and 90 females) could be enrolled in this study. The main demographic and clinical characteristics of the cohort are detailed in Table 1. All patients were virtually anuric (24-hour urine volume <200 mL/day) and were being treated three times a week with standard bicarbonate dialysis (sodium 138 mmol/L, HCO_3 35 mmol/L, potassium 1.5 mmol/L, calcium 1.25 mmol/L, magnesium 0.75 mmol/L) and cuprophan or semisynthetic membranes (dialysis filters surface area 1.1 to 1.7 m^2). One hundred and thirty patients were on

treatment with erythropoietin. Seventy-eight patients were being treated with antihypertensive drugs [54 on monotherapy with angiotensin-converting enzyme (ACE) inhibitors, angiotensin type 1 antagonists, calcium channel blockers, and alpha and beta blockers and 24 on double or triple therapy with various combinations of these drugs).

Patients who repeated the echocardiographic study

Thirty patients out of 203 of the original cohort died before the time at which the second echocardiographic study was performed, four patients underwent renal transplantation and eight patients could not repeat echocardiography for logistic reasons. Therefore, 161 patients were left for this study aimed at defining the prognostic value of changes in LVMI (see Table 1). In the present analysis, we considered the patients who attended the baseline and the second echocardiographic study contemplated in the CREED study.

Follow-up

After the initial assessment, patients were followed-up by the nephrologists participating in the study (CREED investigators). The study was purely observational and therefore it did not contemplate changes in treatment policy. The second echocardiographic study was performed from 13.6 to 22.6 months (average 18 months) after the baseline study.

The overall duration of the follow-up was 39 ± 19 months. The duration of follow-up after the second echocardiographic study was 29 ± 13 months. Since in the present study we were interested in establishing the prognostic value of changes in LVMI, all survival analyses reported herein apply to the follow-up after the second echocardiographic study (see also the **Methods** section, Statistical Analysis).

End point evaluation

During the follow-up cardiovascular events (electrocardiographic-documented anginal episodes and myocardial infarction, heart failure, electrocardiographic-documented arrhythmia, transient ischemic attacks, stroke, and other thrombotic events) and death were accurately recorded. Each death was reviewed and assigned an underlying cause by a panel of five physicians. As a part of the review process, all available medical information about each death was collected. This information always included study and hospitalization records. In the case of an out-of-hospital death family members were interviewed by telephone to better ascertain the circumstances surrounding death. As alluded to before, for the purpose of establishing the prognostic value of LVH progression, only events (death and cardiovascular events) occurring after the second echocardiogram were considered.

Echocardiography

These studies were performed in a nondialysis day within 2 hours after blood sampling (see below). At the time of the echocardiographic examination, investigators involved in echocardiographic studies (F.B. and G.G.) were unaware of patients' clinical data. LVM was calculated according to the Devereux formula and indexed to height$^{2.7}$ (LVMI) [17]. The height-based indexing of LVM was specifically chosen to minimize any potential distortion attributable to extracellular volume expansion (surface area indexing being weight-sensitive) [3]. Mean wall thickness (MWT) was calculated by the standard formula [MWT = (posterior wall thickness + interventricular septum thickness)/2]. The relative wall thickness (RWT) (2 · posterior wall thickness/left ventricular end diastolic diameter) was also calculated, as an index of the left ventricular geometric pattern. Changes in LVMI were quantified by subtracting LVMI at the second study from that obtained at baseline study and by factoring this difference for the time interval between the two studies.

Biochemical measurements

Blood sampling for the measurement of routine and special biochemical measurements were performed before echocardiographic studies. The methods used for the determination of serum C-reactive protein (CRP), plasma norepinephrine, ADMA, and homocysteine were detailed in previous publications [9, 10].

Blood pressure measurements

Blood pressures were calculated as the average value of all recordings [12 measurements (i.e., 3/week)] taken predialysis during the month preceding the study [18].

Statistical analysis

Data are expressed as mean ± SD (normally distributed data), median and interquartile range (nonnormally distributed data) or as percent frequency. Comparisons between groups were made by a test for trend and within subject comparisons by the paired *t* test or the chi-square test, as appropriate. Probability of survival was analyzed using the Kaplan-Meier survival analysis and by the multivariate Cox proportional hazards model. In these analyses patients were divided into three groups on the basis of the 25th and the 75th percentile of LVMI changes. For patients who had multiple events, survival analysis was restricted to the first event. The independent prognostic value of LVMI changes for mortality and cardiovascular events was tested by multivariate Cox regression analysis. Multivariate models

were constructed by starting with all covariates that were associated ($P < 0.05$) with the outcome measures (mortality and cardiovascular events) at univariate Cox regression analysis. To obtain parsimonious models, covariates that independently contributed to the prediction of these outcomes were identified by a backward approach in models where we always forced baseline LVMI. The following covariates were initially considered for these analyses: baseline LVMI and LVMI change, age, gender, diabetes; baseline systolic pressure and heart rate, and their changes from baseline to the follow up visit; previous cardiovascular events, antihypertensive therapy at baseline and follow-up, smoking habits, serum cholesterol, hemoglobin, albumin, Ca × P product, Kt/V, and the change in these covariates at follow-up. Furthermore, we also tested emerging risk factors (CRP, homocysteine, ADMA, and norepinephrine), which were available at baseline visit only. By this approach we constructed models of adequate statistical power (at least 10 events for each variable in the final model). The assumption of linearity for the Cox models was examined through visual inspection and no violation of proportional hazards was found. Missing values (albumin, $N = 4$; Δalbumin, $N = 2$; cholesterol, $N = 4$; Δcholesterol, $N = 8$; calcium × phosphate, $N = 3$; Δcalcium x phosphate, $N = 8$; CRP, $N = 3$; homocysteine, $N = 3$; ADMA, $N = 4$; and Δhemoglobin, $N = 1$) were set at the average value of the corresponding variable. Hazard ratios (HR) and their 95% CI were calculated using the estimated regression coefficients and their standard errors in the Cox regression analysis. All calculations were made using a standard statistical package (SPSS for Windows, version 9.0.1, Chicago, IL, USA).

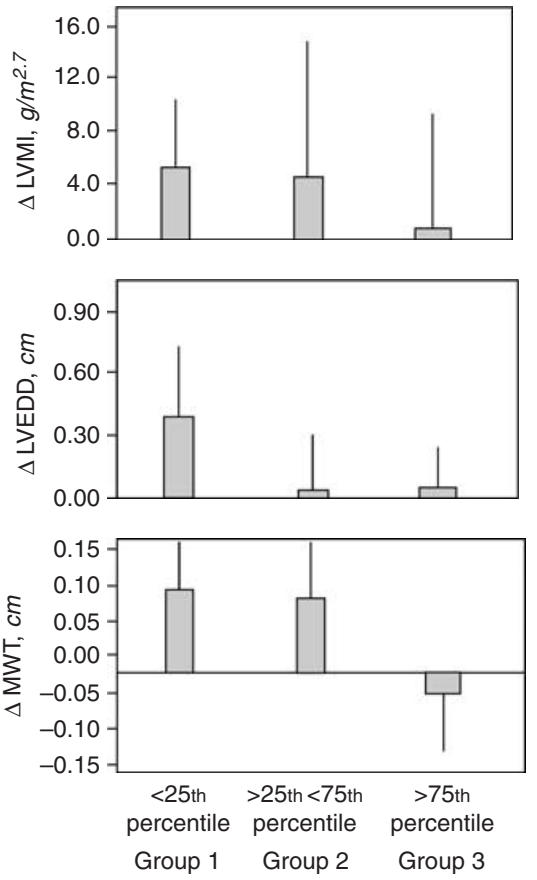

Fig. 1. Relationship between baseline echocardiographic measurements of the left ventricle and their changes at the second examination. Abbreviations are: LVMI, left ventricular mass index; LVEDD, left ventricular end diastolic diameter; MWT, mean wall thickness.

RESULTS

The main somatometric, clinical, hemodynamic, biochemical and echocardiographic data at the baseline and at the second echocardiographic study are shown in Table 1. Arterial pressure showed a minor reduction. Hemoglobin, serum cholesterol and the administered dialysis dose (Kt/V) improved significantly while serum albumin showed a 14% decrease. Overall, there was a significant worsening in LVMI and in all anatomic parameters of the left ventricle while left ventricular ejection fraction did not change. Figure 1 shows absolute changes in echocardiographic parameters as related to their relative baseline measurements. LVMI changes as well as changes in the other echocardiographic parameters were more pronounced in patients in the first group (i.e., those with values <25th percentile) and declined consistently from the first to the third group (those with values >75th percentile). This phenomenon indicates that the baseline measurement is a confounder for subsequent changes. In other words, changes were much attenuated in patients with initially higher values because, due to the phenomenon of the regression to the mean, extreme values tend to be less extreme repeated measurements. Thus in patients with higher initial LVMI the appreciation of any progression in LVH (a biologic phenomenon) is attenuated by a purely statistical phenomenon of opposite sign (regression to the mean).

LVH progression, all-cause death, and cardiovascular morbidity: Kaplan-Meier analysis

After the second echocardiographic study, 58 patients died. Sixty-six patients had one or more cardiovascular events, which were fatal in 45 cases. The rate of increase in LVMI was higher ($P = 0.01$) in patients who died during the follow-up (median 0.25 g/m$^{2.7}$/month, interquartile range 0.08 to 0.72 g/m$^{2.7}$/month) than in those who survived (0.15 g/m$^{2.7}$/month, −0.16 to 0.44 g/m$^{2.7}$/month) and in a Kaplan-Meier analysis there was a graded relationship between the rate of increase in LVMI and the incidence of death so that the relative risk of patients with ΔLVMI >75th percentile (HR 2.56, 95% CI 1.94–3.31) was substantially higher than that of patients with

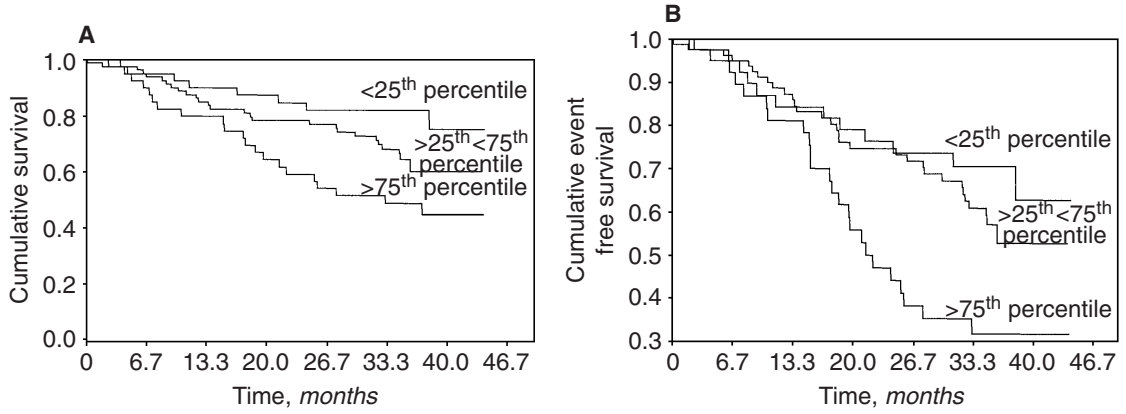

Fig. 2. Kaplan-Meier curves for all-cause mortality (*A*) and for fatal and nonfatal cardiovascular events (*B*). Patients were divided into three groups on the basis of the 25th and the 75th percentile of left ventricular mass index (LVMI) changes.

Table 2. Multivariate analysis of all-cause death

	Units of increase	Hazard ratio (95% CI)	*P* value
Changes in LVMI			
<25th percentile	<-0.10 g/m$^{2.7}$/month	1[a]	
25–75th percentile	-0.10- 0.50 g/m$^{2.7}$/month	1.60 (0.70–3.66)	0.26
>75th percentile	>0.50 g/m$^{2.7}$/month	3.07 (1.34–7.05)	0.008
Age	1 year	1.05 (1.03–1.08)	<0.001
Male gender		2.42 (1.36–4.34)	0.003
Previous cardiovascular events[b]		1.58 (0.91–2.72)	0.10
Baseline LVMI		1.01 (0.99–1.03)	0.12

LVMI is left ventricular mass index; ADMA is asymmetrical dimethylarginine.
[a]Reference group.
[b]Events occurring in between the two echocardiographic studies were considered (together with cardiovascular events that occurred before the study) as "previous cardiovascular events" and the variable was introduced into the multivariable analysis.

ΔLVMI <25th percentile (log rank test 8.06, $P = 0.004$) (Fig. 2A). Similarly, the rate of increase in LVMI was significantly higher ($P = 0.029$) in patients with incident fatal and nonfatal cardiovascular events (0.25 g/m$^{2.7}$/month, 0.04 to 0.71 g/m$^{2.7}$/month) than in those without such events (0.14 g/m$^{2.7}$/month, -0.16 to 0.44 g/m$^{2.7}$/month). Accordingly, the relative risk of adverse cardiovascular outcomes was s higher (HR 2.01, 95% CI 1.46–2.54) in patients with changes in LVMI above the 75th percentile than in those with changes below the 25th percentile (log rank test 8.31, $P = 0.004$) (Fig. 2B).

LVH progression, all-cause death, and cardiovascular morbidity: Univariate and multivariate Cox regression analysis

On univariate analysis, besides changes in LVMI, also age, gender, smoking, previous cardiovascular events, baseline LVMI and plasma norepinephrine resulted to be significantly associated to incident all cause mortality (all $P < 0.05$). When we tested the predictive power of all univariate predictors of survival by a backward elimination strategy, only variables listed in Table 2 maintained an independent association with the outcome. In this model we forced also baseline LVMI to control for regression to the mean. By this analysis we found that the progression of LVH was significantly related to all-cause mortality (Table 2). By the same token, changes in LVMI resulted to be an independent predictor of fatal and nonfatal cardiovascular events in a Cox model, including age, smoking, diabetes, previous cardiovascular events, baseline LVMI, and plasma ADMA (Table 3).

DISCUSSION

This study shows that progression of LVH in patients with ESRD is associated with mortality and incident cardiovascular events independently of baseline LVM and of traditional and emerging risk factors. This finding indicates that monitoring LVM by echocardiography provides significant prognostic information respect to a single estimate of LVM and suggests that repeated measurements may be useful in clinical practice in the management of ESRD patients. LVH is perhaps the most powerful indicator of mortality and cardiovascular complications in patients with chronic renal failure [5]. Several mechanisms may contribute to explain the increased risk associated with LVH. LVH is associated with myocardial fibrosis and diastolic dysfunction which is an important factor in the evolution of heart failure. Furthermore

Table 3. Multivariate analysis of fatal and nonfatal cardiovascular events

	Units of increase	Hazard ratio (95% CI)	*P* value
Changes in LVMI			
<25th percentile	<-0.10 g/m$^{2.7}$/month	1[a]	
25–75th percentile	-0.10- 0.50 g/m$^{2.7}$/month	1.48 (0.73–2.99)	0.28
>75th percentile	>0.50 g/m$^{2.7}$/month	3.02 (1.44–6.34)	0.003
Age	1 year	1.04 (1.02–1.06)	<0.001
Smoking		1.95 (1.18–3.25)	0.01
Diabetes		2.55 (1.33–4.91)	0.005
Previous cardiovascular events[b]		1.78 (1.08–2.93)	0.02
Baseline LVMI		1.00 (0.99–1.01)	0.97
ADMA	1 μmol/L	1.20 (1.04–1.38)	0.01

LVMI is left ventricular mass index; ADMA is asymmetrical dimethylarginine.
[a]Reference group.
[b]Events occurring in between the two echocardiographic studies were considered (together with cardiovascular events that occurred before the study) as "previous cardiovascular events" and this variable was introduced into the multivariable analysis.

LVH reduces coronary reserve and induces cardiac ischemia which may in turn promote myocardial infarction and lethal arrhythmias. The problem of whether progression or regression of LVH predicts clinical outcomes is an important issue in clinical practice because it could signal an increasing level of risk and may prompt a better tailoring of treatments being administered and/or a closer surveillance. The prognostic importance of changes in LVM has been established in observational studies in the general population [13] and in essential hypertensive patients [14] as well as in the context of large randomized clinical trials [19]. Thus progression and reversal of LVH are solidly linked to parallel changes in major cardiovascular complications in the general population. The prognostic value of changes in LVM in ESRD in everyday clinical practice is still unknown. The issue is important because, due to the difference in risk factors and in background cardiovascular complications [20], results of studies in the general population cannot be loosely applied to the dialysis population. An elegant multifactorial intervention trial by London et al [4] has demonstrated that LVH regression is strongly associated with reduced mortality in dialysis patients. In clinical practice, adherence to treatment and clinical monitoring are much less accurate than during clinical trials and it is well known that patients enrolled in clinical trials may not be representative of the parent population. Although inferior to clinical trials to assess the efficacy of treatments, observational studies provide prognostic information which better reflect the real world of everyday clinical practice. In the context of clinical practice in ESRD patients the prognostic value of changes in LVM cannot be taken for granted. Indeed, LVH progression was associated with a difference of marginal statistical significance in the incidence rate of cardiac failure in an observational study by Foley et al [12], while there is presently no observational study linking LVH progression to mortality in ESRD patients. In testing the prognostic value of repeated measurements of any putative risk factor or risk marker it is important accounting for the baseline estimate of the factor being tested. Indeed, owing to measurement error, extreme values tend to be less extreme when the measurement is replicated (regression to the mean), a phenomenon that was very evident in our cohort. The fact that progression of LVH was strongly linked to subsequent mortality and cardiovascular events independently of baseline LVMI and of a large series of traditional and emerging risk factors is of relevance because it indicates that assessing changes in LVMI is at least as important as estimating LVMI. Like in the study by Foley et al [12], we found that LVH worsens with time. Indeed, in our cohort LVMI increased by 7% in the second study performed about $1^1/_2$ years after the baseline study. This finding indicates that management of risk factors for LVH was unsatisfactory in our patients and that there is ample room for improvement. Our analysis coherently suggests that changes in LVM represent a stronger predictor for mortality and CV complications than LVMI itself and suggests that periodic echocardiographic studies are useful in patients with ESRD. Our study has limitations. Due to mortality and censoring, about 25% of patients could not repeat echocardiography. Thus, the cohort that entered the follow-up study aimed at establishing the prognostic value of serial echocardiographic studies had a lower risk than the original cohort and therefore it imperfectly reflects risk factors for LVH in the dialysis population. A shorter time interval between the two echocardiographic studies could have limited this problem but the shorter the time interval the less likely registering meaningful changes in LVMI in the absence of an articulated intervention plan. Thus, our study suggests that repeating echocardiography after about $1^1/_2$ years is useful for risk stratification but it remains to be studied whether shorter echocardiographic monitoring of LVM conveys comparable prognostic information.

The second limitation derives from the fact that LVMI measurements in the CREED cohort were made by two cardiologists who carefully calibrated

echocardiographic measurements on the basis of established standards. In clinical practice echocardiographic measurements of LVMI made by different sonographers in different institutions may be less reliable. Furthermore, it still remains to be demonstrated that repeated LVMI measurements have a favorable impact in the management of ESRD. The efficacy of a clinical policy contemplating serial LVMI measurements in ESRD patients remains to be formally tested in a randomized clinical trial, which is the gold standard for establishing the value of clinical tests.

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