Intensive Home Hemodialysis Results in Regression of Left Ventricular Hypertrophy and Better Clinical Outcomes

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Key Words

Intensive hemodialysis · Home hemodialysis · Left ventricular mass · Left ventricular hypertrophy · Regression

Abstract

Background: Left ventricular hypertrophy (LVH) is an independent risk factor for mortality and cardiovascular events in patients with end-stage renal disease. Studies have shown that frequent hemodialysis leads to LVH regression, but the impact of left ventricular mass (LVM) regression on clinical outcomes remains unknown. **Methods:** This observational cohort study assessed the impact of LVH regression on the composite outcome of time to all-cause mortality, technique failure or cardiovascular hospitalization in patients on home hemodialysis. LVH regression was defined as either a reduction of more than 10% in LVM in patients with LVH at baseline or prevention of LVH in those without LVH at baseline. Risk factors associated with progression of LVM were also examined. **Results:** We studied 144 intensive hemodialysis patients between 1999 and 2012 with a mean follow-up of 4.7 years. Eighty-seven patients (60.4%) had LVH regression or prevention and 57 patients (39.6%) had LVH progression. In a multivariate analysis, smoking (OR 2.78, 95% CI 1.06–7.36) and presence of LVH at baseline (OR 2.21, 95% CI 1.06–4.59) were significant predictors for LVM progression. Sixteen patients (18.4%) in the regressor group and 19 patients

(33.3%) in the progressor group developed the composite end point. When adjusted for age and diabetes, regression was significantly associated with a decreased risk (hazards ratio (HR) 0.42, 95% CI 0.21–0.84) for the composite end point. Regression was also significantly associated with a decreased risk of death in the adjusted analysis (HR 0.20, 95% CI 0.06–0.67). **Conclusions:** Regression of LVH with intensive hemodialysis is associated with favorable clinical outcomes.

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Introduction

Cardiovascular disease remains the leading cause of morbidity and mortality among end-stage renal disease (ESRD) patients, accounting for 38% of all fatalities [1, 2]. There has been increasing evidence that left ventricular hypertrophy (LVH) is an independent risk factor for mortality and cardiovascular events with important prognostic value in the ESRD population [3–5]. In fact, LVH increases in prevalence with progressive renal function decline, present in up to 85% of incident dialysis patients [6–8]. LVH in ESRD is multifactorial in origin; hypertension, vascular calcification, volume overload, anemia, hyperparathyroidism, inflammation, high sympathetic activity and various other metabolic and humoral changes having all been implicated in the pathophysiology [2, 4, 5, 9–13].

Studies in conventional hemodialysis and peritoneal dialysis have shown that LVH progresses with time in most patients [4, 14, 15]. In contrast, there has been many studies in recent years demonstrating that frequent hemodialysis (short-daily or long-nocturnal) leads to LVH regression along with improvements in blood pressure control, abnormalities of mineral metabolism, sleep quality and quality of life [16–21]. In the Frequent Hemodialysis Network Daily Trial, 245 patients were randomized to 6X/week (short-daily or nocturnal) or 3X/week hemodialysis [22]. Left ventricular mass (LVM), measured by cardiac MRI, decreased with frequent hemodialysis compared to control in both daily and nocturnal trials, although a significant difference was observed only in the larger short-daily group, likely owing to the larger sample size [22].

Several studies have demonstrated improved clinical outcomes with LVH regression in different patient populations. In fact, in 161 in-center hemodialysis patients, Zoccali et al. [4] showed a graded relationship between the rate of increase in LVM and adverse outcomes, with a 1 g/m^{2.7}/month increase in LVM index (LVMI) associated with a 62% increased risk of fatal and nonfatal cardiovascular events. London et al. [23] also demonstrated that the regression of LVM had a favorable impact on survival in conventional hemodialysis patients, with a 10% LVM decrease associated with decreased all-cause and cardiovascular-related mortality. Furthermore, a meta-analysis in patients with hypertension also showed that LVH regression was independently associated with a reduction in cardiovascular events [24]. Similarly, a recent study in renal transplant recipients also showed improved outcomes with LVH regression [25]. However, the impact of regression of LVM in the setting of more frequent intensive hemodialysis remains unknown.

Objective

The purpose of this study was to determine whether regression of LVH with intensive home hemodialysis is associated with improved clinical outcomes and to examine the different risk factors associated with regression or progression of LVM.

Methods

We performed a retrospective cohort study in patients on intensive home hemodialysis at the Toronto General Hospital from January 1, 1999, to July 1, 2012. Exclusion criteria included patients on home hemodialysis for <1 year or patients with missing echocardiographic information at baseline or upon follow-up. In-

tensive hemodialysis was defined as ≥16 h of hemodialysis therapy per week based on the prescribed regimen on the last day of home hemodialysis training. A standard initial regimen consisted of ≥5 nocturnal sessions of hemodialysis per week of at least 7 h duration. We then classified patients based on regression or progression of LVH in their following echocardiograms.

Echocardiograms, performed before a hemodialysis session, were done at baseline and subsequently at yearly intervals. LVM measurements included the LV posterior wall thickness, interventricular septal thickness and mean wall thickness calculated by the 2D method. LVH was defined using the recent recommendations from the American Society of Echocardiography and European Association of Cardiovascular Imaging – a LVMI >102 g/m² in men and >88 g/m² in women – measured using the 2D method [26].

Regression of LVH ('regressors') was defined as a reduction of more than 10% in LVM in the last follow-up echocardiogram in patients with LVH at baseline, and continued absence of LVH in patients without LVH at baseline. Progression of LVH ('progressors') was defined as a reduction of less than 10% or increase in LVM in the last follow-up echocardiogram in patients with LVH at baseline, and development of LVH in the last follow-up echocardiogram in patients without LVH at baseline. A 10% cutoff was used to define regression as London et al. [23] previously demonstrated favorable outcomes with a 10% LVM decrease in hemodialysis patients.

The primary outcome was the composite outcome of time to all-cause mortality, technique failure or cardiovascular hospitalization from the initiation of the modality. Technique failure was defined as a permanent switch to another renal replacement modality (conventional hemodialysis or peritoneal dialysis), and a cardiovascular event was defined as either myocardial infarction or unstable angina or arrhythmia or heart failure or stroke.

Covariates considered to be critically relevant included age, gender, race, body mass index, cause of ESRD, duration of ESRD, first vascular access type, type of renal replacement therapy prior to intensive hemodialysis and coexisting medical conditions (diabetes, smoking, coronary artery disease, hypertension, cerebrovascular disease and peripheral vascular disease). Antihypertensive therapies at baseline and after 1 year of intensive hemodialysis were also documented.

Statistical Analysis

Baseline demographics and clinical characteristics are presented as means ± SD or proportions, as appropriate. Comparisons were tested using the chi-square or Fisher's exact test for categorical variables, and Student t test for continuous variables. Kaplan-Meier plots are presented to evaluate the time to composite outcome (death, treatment failure or cardiovascular hospitalization) in regressors and progressors. To provide an estimate of LVH regression on clinical outcome after adjustment for other variables, a Cox regression model was used. *p* values of <0.05 were considered statistically significant. All analyses were performed using SPSS version 20.0 (IBM Corp., USA).

Results

A total of 144 patients were included in our cohort after excluding the following patients: <1-year follow-up (*n* = 31) and missing echocardiogram information (*n* =

Fig. 1. Patient flow diagram is illustrated.

42). Figure 1 illustrates the patient flow diagram. The mean follow-up was 4.7 ± 3.0 years. The baseline demographics of the cohort are summarized in table 1.

LVH Status at Baseline

At baseline, 82 patients (56.9% of the cohort) had LVH. Baseline characteristics of patients with and without LVH at time of initiation of intensive hemodialysis are presented in table 2. Patients with LVH were older (mean age 46.6 vs. 41.3 years, $p = 0.013$), more likely to have had a failed kidney transplant as a cause for ESRD (29.3 vs. 14.5%, $p = 0.029$) and more likely to be diabetic (28.0 vs. 14.5%, $p = 0.050$). Patients with LVH were also treated with a higher number of antihypertensive medications (mean 2.03 vs. 1.44, $p = 0.020$) with a higher proportion of patients on >2 drugs (65.8 vs. 41.0%, $p = 0.003$). All other baseline characteristics were not significantly different.

Regressors vs. Progressors

After follow-up, 87 patients (60.4%) developed LVH regression or prevention and 57 patients developed LVH progression (39.6%). Characteristics of regressors and progressors are presented in table 3. Progressors were

more likely to have LVH at baseline (68.4 vs. 49.4%, $p = 0.024$). In fact, in patients without LVH at baseline, there were 18 progressors (29.0%) while, in patients with LVH at baseline, there were 39 progressors (47.6%). Progressors were also more likely to be smokers (22.8 vs. 9.2%, $p = 0.024$). In regards to antihypertensive therapy, while there was a non-statistically significant higher proportion of progressors on >2 drugs at baseline, antihypertensive therapy was not different between both groups after 1 year on intensive hemodialysis. In fact, 81.2% of regressors and 81.5% of progressors either achieved a decrease in number of antihypertensive drugs or remained off blood pressure medications. Similar, only 21.2% of the regressors and 18.5% of the progressors remained on >2 drugs compared to 48.8 and 64.8%, respectively, at baseline. All other baseline characteristics were not significantly different between both groups. The mean rate of regression was -14.1 ± 12.2 g per year in regressors with LVH at baseline.

In a multivariate analysis, smoking history (OR 2.78, 95% CI 1.06–7.36, $p = 0.039$) and presence of LVH at baseline (OR 2.21, 95% CI 1.06–4.59, $p = 0.033$) were significant predictors for progression (table 4). Age and diabetes were not significant predictors.

Effect of LVH Regression on Clinical Outcomes

Sixteen patients (18.4%) in the regressors group as compared 19 patients (33.3%) in the progressors group developed the composite end point of death, technique failure or cardiovascular hospitalization. Four deaths (4.6%) occurred in the regressors group while 9 deaths (17.5%) occurred in the progressors group. Four patients (4.6%) experienced technique failure in the regressors group compared to 7 patients (12.3%) in the progressors. In regards to cardiovascular hospitalization, 8 patients (9.2%) experienced this end point in the regressors compared to 6 patients (10.5%) in the progressors. A total of 43 patients were transplanted during the time of follow-up (32.2% of the regressors and 26.3% of the progressors). Kaplan–Meier curves with log-rank test showed improved survival in patients with LVH regression compared to progression with regards to both the composite outcome ($p = 0.046$; fig. 2) and death ($p = 0.009$; fig. 3).

In an unadjusted Cox regression analysis, LVH regression was significantly associated with a lower risk of the primary composite outcome (hazard ratio (HR) 0.51, 95% CI 0.26–0.99). When adjusted for age and diabetes, LVH regression remained significantly associated with a decreased risk (HR 0.42, 95% CI 0.21–0.84) while age (HR

Table 1. Baseline characteristics of the cohort

Age, years, mean $\pm$ SD	44.3 $\pm$ 12.9
Male sex, n (%)	91 (63.2)
Race, n (%)	
White	88 (61.1)
Asian	18 (12.5)
Black	12 (8.3)
Other	26 (18.1)
BMI, kg/m ² , mean $\pm$ SD	25.4 $\pm$ 6.2
Cause of ESRD, n (%)	
Diabetic nephropathy	19 (13.2)
Glomerulonephritis	47 (32.6)
Hypertensive nephrosclerosis	8 (5.6)
Polycystic kidney disease	12 (8.3)
Other	58 (40.3)
Type of renal replacement therapy prior to intensive hemodialysis, n (%)	
Chronic kidney disease not on dialysis	41 (28.5)
Non-intensive hemodialysis	61 (42.4)
Peritoneal dialysis	9 (6.2)
Renal transplantation	33 (22.9)
Initial access type, n (%)	
CVC	67 (46.5)
AVF	69 (47.9)
AVG	8 (5.6)
Duration of ESRD, years, mean $\pm$ SD	6.5 $\pm$ 8.4
Presence of LVH at baseline, n (%)	82 (56.9)
LVM at baseline, g, mean $\pm$ SD	196.4 $\pm$ 71.0
LVMi at baseline, g/m ² , mean $\pm$ SD	108.1 $\pm$ 36.4
Co-existing medical conditions, n (%)	
Diabetes	32 (22.2)
Smoking history	21 (14.6)
Hypertension	122 (84.7)
Coronary artery disease	17 (11.8)
Peripheral vascular disease	9 (6.2)
Stroke	11 (7.6)
Baseline blood pressure therapy	
Number of antihypertensives, mean $\pm$ SD	1.77 $\pm$ 1.43
Patients on >2 antihypertensives, n (%)	77 (55.0)
RAAS blockade/CCB/ β -blocker, %	43.6/49.3/50.7
1-Year blood pressure therapy	
Number of antihypertensives, mean $\pm$ SD	0.73 $\pm$ 0.94
Patients on >2 antihypertensives, n (%)	28 (20.1)
RAAS blockade/CCB/ β -blocker, %	18.7/13.6/37.4

1.04, 95% CI 1.01–1.07) and diabetes (HR 2.78, 95% CI 1.32–5.82) were significant predictors of developing the composite end point (table 5).

On the basis of mortality alone, LVH regression was also significantly associated with a decreased risk of death in the unadjusted analysis (HR 0.24, 95% CI 0.08–0.77) and this remained significant after adjustment for age and diabetes (HR 0.20, 95% CI 0.06–0.67; table 6).

Discussion

The present study is the first study to demonstrate that regression of LVH leads to favorable clinical outcomes in patients on intensive home hemodialysis. In fact, our study showed that patients on home hemodialysis with regression or prevention of LVH had a 58% lower risk of the composite end point of death, technique failure or cardiovascular hospitalization during a mean follow-up of 4.7 years compared with patients with progression or development of LVH. With regards to mortality alone, LVH regression was associated with an 80% decreased risk. Improved survival associated with regression also occurred later suggesting that the time for cardiac remodeling to occur with LVM regression led to a favorable long-term mortality benefit.

Furthermore, regression or prevention of LVH was seen in about two-thirds of patients after initiation of home hemodialysis. In fact, in patients without LVH at baseline, 29.0% of patients progressed to developing LVH, in contrast to 47.6% of patients with the presence of LVH at baseline. The significant risk factors identified for LVM progression were the presence of baseline LVH and smoking history. While there was a non-significant trend of a higher proportion of patients with >2 antihypertensive drugs at baseline in the progressors group, this is likely related to the higher proportion of patients with baseline LVH. In fact, after 1 year of intensive hemodialysis, both groups achieved a similar significant reduction in the use of antihypertensive medications, thus suggesting that progression or regression of LVH was mediated by factors independent of blood pressure in this cohort.

These results highlight the important prognostic implication of LVH regression or prevention in patients on intensive home hemodialysis, regardless of therapeutic strategy. Our study also emphasizes the clinical relevance of serial measurements of LVM in these patients. Moreover, our results show that LVH regression or prevention may be achieved in a substantial proportion of patients with intensive more frequent hemodialysis, regardless of renal replacement therapy modality prior to initiation. These results are also consistent with other studies demonstrating improved LVM with intensive hemodialysis [16, 20–22]. This is in contrast to studies in peritoneal dialysis or conventional hemodialysis, which have shown that LVH develops and progresses in the majority of patients with time [4, 14]. The present study's finding of an independent and strong association between LVH regression and improved clinical outcomes is equally comple-

Table 2. Characteristics of patients with and without LVH at baseline

	No LVH at baseline (n = 62)	LVH at baseline (n = 82)	p value
Age, years, mean $\pm$ SD	41.3 $\pm$ 13.3	46.6 $\pm$ 12.2	0.013
Male sex, n (%)	40 (64.5)	51 (62.2)	0.775
BMI, kg/m ² , mean $\pm$ SD	25.3 $\pm$ 6.4	25.5 $\pm$ 6.1	0.890
Type of renal replacement therapy prior to intensive hemodialysis, n (%)			0.029
Chronic kidney disease not on dialysis	21 (33.9)	20 (24.4)	
Non-intensive hemodialysis	25 (40.3)	36 (43.9)	
Peritoneal dialysis	7 (11.3)	2 (2.4)	
Renal transplantation	9 (14.5)	24 (29.3)	
Initial access type, n (%)			0.697
CVC	30 (48.4)	37 (45.1)	
AVF or AVG	32 (51.6)	45 (54.9)	
Duration of ESRD, years, mean $\pm$ SD	5.5 $\pm$ 7.7	7.4 $\pm$ 8.9	0.176
Co-existing medical conditions, n (%)			
Diabetes	9 (14.5)	23 (28.0)	0.050
Smoking history	7 (11.3)	14 (17.1)	0.330
Hypertension	51 (82.3)	71 (86.6)	0.475
Coronary artery disease	5 (8.1)	12 (14.6)	0.226
Peripheral vascular disease	2 (3.2)	7 (8.5)	0.192
Stroke	5 (8.1)	6 (7.3)	0.867
Baseline blood pressure therapy			
Number of antihypertensives, mean $\pm$ SD	1.44 $\pm$ 1.58	2.03 $\pm$ 1.25	0.020
Patients on >2 antihypertensives, n (%)	25 (41.0)	52 (65.8)	0.003

Table 3. Characteristics of patients with LVH regression and progression

	Regressors (n = 87)	Progressors (n = 57)	p value
Age, years, mean $\pm$ SD	44.2 $\pm$ 12.1	44.5 $\pm$ 14.2	0.881
Male sex, n (%)	56 (64.4)	35 (61.4)	0.718
BMI, kg/m ² , mean $\pm$ SD	25.5 $\pm$ 6.1	25.3 $\pm$ 6.4	0.901
Type of renal replacement therapy prior to intensive hemodialysis, n (%)			0.742
Chronic kidney disease not on dialysis	24 (27.6)	17 (29.8)	
Non-intensive hemodialysis	36 (41.4)	24 (43.9)	
Peritoneal dialysis	7 (8.0)	2 (3.5)	
Renal transplantation	20 (23.0)	13 (22.8)	
Initial access type, n (%)			0.122
CVC	45 (51.7)	22 (38.6)	
AVF or AVG	42 (48.3)	35 (61.4)	
Duration of ESRD, years, mean $\pm$ SD	6.9 $\pm$ 8.6	5.9 $\pm$ 8.1	0.488
Presence of LVH at baseline, n (%)	43 (49.4)	39 (68.4)	0.024
LVM at baseline, g, mean $\pm$ SD	190.1 $\pm$ 75.7	205.8 $\pm$ 62.7	0.302
LVMi at baseline, g/m ² , mean $\pm$ SD	105.6 $\pm$ 39.7	112.1 $\pm$ 30.7	0.196
Co-existing medical conditions, n (%)			
Diabetes	19 (21.8)	13 (22.8)	0.891
Smoking history	8 (9.2)	13 (22.8)	0.024
Hypertension	71 (81.6)	51 (89.5)	0.200
Coronary artery disease	9 (10.3)	8 (14.0)	0.502
Peripheral vascular disease	6 (6.9)	3 (5.3)	0.692
Stroke	8 (9.2)	3 (5.3)	0.385
Baseline blood pressure therapy			
Number of antihypertensives, mean $\pm$ SD	1.65 $\pm$ 1.52	1.96 $\pm$ 1.26	0.209
Patients on >2 antihypertensives, n (%)	42 (48.8)	35 (64.8)	0.064
1-Year blood pressure therapy			
Number of antihypertensives, mean $\pm$ SD	0.69 $\pm$ 0.91	0.80 $\pm$ 1.00	0.536
Patients on >2 antihypertensives, n (%)	18 (21.2)	10 (18.5)	0.703
No antihypertensives or less than baseline, n (%)	69 (81.2)	44 (81.5)	0.964

Table 4. Multivariate analysis for the development of LVH progression

Variable	Unadjusted OR (95% CI)	p value	Adjusted OR (95% CI)	p value
Age	1.00 (0.98–1.03)	0.880	0.99 (0.97–1.03)	0.755
Diabetes	1.06 (0.48–2.36)	0.891	0.93 (0.39–2.22)	0.877
Smoking history	2.92 (1.12–7.58)	0.028	2.78 (1.06–7.36)	0.039
LVH at baseline	2.21 (1.10–4.46)	0.026	2.21 (1.06–4.59)	0.033

Table 5. Cox proportional hazards analysis of the risk of the composite end point of death, technique failure and CV-related hospitalization

Variable	Unadjusted OR (95% CI)	p value	Adjusted OR (95% CI)	p value
LVH regressors vs. progressors	0.51 (0.26–0.99)	0.050	0.42 (0.21–0.84)	0.014
Diabetes	3.25 (1.62–6.53)	0.001	2.78 (1.32–5.82)	0.007
Age	1.05 (1.02–1.08)	0.001	1.04 (1.01–1.07)	0.009

Table 6. Cox proportional hazards analysis of the risk of the death

Variable	Unadjusted OR (95% CI)	p value	Adjusted OR (95% CI)	p value
LVH regressors vs. progressors	0.24 (0.08–0.77)	0.017	0.20 (0.06–0.67)	0.009
Diabetes	2.78 (0.93–8.35)	0.069	2.74 (0.85–8.86)	0.093
Age	1.06 (1.02–1.11)	0.004	1.05 (1.01–1.10)	0.017

Fig. 2. Composite end point-free survival in LVH regressors and progressors. Regressors had a significantly lower risk of developing the composite end point. **Fig. 3.** Patient survival in LVH regressors and progressors. Regressors had a significantly lower risk of mortality.

mented by similar studies in patients on conventional hemodialysis, with essential hypertension and renal transplant recipients [4, 23–25, 27, 28].

There are many potential pathophysiologic mechanisms for worsened clinical outcomes with LVM progres-

sion. Indeed, there has been consistent evidence that progressive LVH and cardiac fibrosis leads to diastolic and systolic dysfunction with chamber dilation, disturbances in intraventricular conduction and changes in ventricular contractility secondary to neurohumoral activation due

to sympathetic activation with increased risk of ventricular arrhythmias [5, 29]. This may consequently predispose to cardiovascular events and sudden cardiac death, which are the leading causes of morbidity and mortality in dialysis patients [1]. In addition, augmenting dialysis frequency has been shown to reduce left and right ventricular volumes and to increase heart rate variability due to changes in vagal modulation of heart rate [30, 31]. In fact, higher ventricular volumes and reduced heart rate variability have both been established as independent risk factors for mortality and cardiovascular events [32, 33].

Reduction of LVM with intensive frequent hemodialysis is likely multifactorial in the context of improved clearance, better control of systemic blood pressure and volume status and abnormalities of mineral metabolism. In fact, all these factors have been shown to improve with increased dialysis frequency and duration [16, 18, 19, 34, 35]. Studies have also demonstrated that intensive hemodialysis leads to downregulation of genes involved in cardiomyocyte apoptosis and fibrosis, decreased arterial stiffness and improved endothelial dysfunction [36, 37].

Our study does have limitations given its observational single-center nature. While the cohort included 144 patients on intensive hemodialysis, the overall sample size could have limited the significance of other potential risk factors for LVH regression. Another limitation is the use of a surrogate composite end point as the primary outcome, which was chosen given the low number of deaths in the follow-up period. The lower mortality rates could be potentially explained by the fact that we excluded patients who died within the first year of initiation of dialysis, a period of increased mortality and patients with missing echocardiographic examinations. In fact, in the excluded patients, there were 16 deaths (21.9%) and 10 technique failures (13.7%). Thus, it is possible that the effect size may be underestimated given that patients who died or had technique failure did not have follow-up echo-

cardiograms. Furthermore, technique failure was included in the composite outcome as it is a surrogate of frailty and comorbid burden. Nonetheless, even when evaluating mortality alone, the positive impact of LVH regression remained significant. Moreover, the use of echocardiography as the imaging modality may have led to overestimation of LVM, and in fact, cardiac MRI would have been a preferred modality [38]. We also did not evaluate the impact of ventricular volume changes. Furthermore, it should be noted that the true hemodialysis frequency and duration could differ from the prescribed regimen given the operator dependence; this could potentially influence our results and is difficult to account for.

Nonetheless, this is the first study evaluating the impact of LVM regression on mortality and cardiovascular events in a cohort of patients on intensive hemodialysis. Indeed, while previous studies have shown that regression of LVM is certainly feasible with longer frequent hemodialysis, we identified that progression or development of LVH was an independent risk factor for mortality, technique failure and adverse cardiac events. In summary, regression of LVH, regardless of the intervention, leads to favorable clinical outcomes in patients on intensive hemodialysis and should be considered a crucial goal. The importance of serial monitoring of LVM is also emphasized. A prospective multi-center study evaluating the impact of changes in LVM would allow for better identification of risk factors for LVH progression and potential therapeutic strategies.

Disclosure Statement

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