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Is Left Ventricular Hypertrophy a Modifiable Risk Factor in ESRD

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Abstract

Purpose of Review—Left ventricular hypertrophy (LVH) is common in ESRD and has been advocated as a therapeutic target. We review considerations for targeting LVH as a modifiable risk factor in ESRD.

Recent Findings—Pathologic myocardial changes underlying LVH provide an ideal substrate for the spread of arrhythmia and may be key contributors to the occurrence of sudden death in ESRD. LVH is present in 68–89% of incident hemodialysis patients and is frequently progressive, although regression is observed in a minority of patients. Higher degrees of baseline LVH as well as greater increases in left ventricular mass index over time are associated with decreased survival, but whether these association are causal remains uncertain. Several interventions including angiotensin blockade and frequent dialysis can reduce left ventricular mass index but whether the associated decrease in left ventricular mass index is associated with improves survival has not been definitively demonstrated.

Summary—LVH is a highly prevalent and reversible risk factor which holds promise as a novel therapeutic target in ESRD. Interventional trials are needed to provide additional evidence that LVH regression improves survival before prevention and reversal of LVH can be definitively adopted as a therapeutic paradigm in ESRD.

Keywords

LVH; ESRD; Cardiovascular; Sudden cardiovascular death

Introduction

Mortality in dialysis dependent end stage renal disease (ESRD) remains high with only 52% of hemodialysis (HD) and 61% of peritoneal dialysis (PD) patients alive 3 years after initiation¹. The high mortality remains incompletely explained but it is dramatically higher than for individuals with preserved renal function and similar degrees of comorbidity. To wit, age, sex and comorbidity adjusted mortality rates were 241 per 1000 patient-years in the prevalent ESRD population in 2011 compared with adjusted rates of 109 and 71 per 1000 patient-years among general Medicare patients with cancer or diabetes, respectively¹.

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Cardiovascular disease (CVD) is an important contributor and accounts for 42.0% of all fatalities¹. However, in contrast to other populations, myocardial infarction accounts for only a minority of CV deaths with the majority attributed to sudden cardiac death (SCD)—an event that occurs at a rate of 49/1000 patient-years among HD patient and 36/1000-patient years among individuals on PD.

This has motivated a tremendous interest in identifying therapeutic strategies with the potential to improve survival, and prevention of CV death, unsurprisingly, has become a major target. Standard CVD therapies, particularly those targeting coronary atherosclerosis, have thus far not provided satisfactory results. To wit, three large trials randomizing more than 7000 dialysis patients to statins or placebo failed to significantly impact mortality despite the consistently beneficial results of statins in other settings²⁻⁴. In light of the unique pathophysiology and epidemiology of CVD in CKD⁵ and disproportionate risks of SCD compared with myocardial infarction/coronary death, the disappointing results of anti-atherosclerotic therapy (with statins) in ESRD suggests that future efforts to improve survival should focus SCD prevention. In this manuscript we review the role of left ventricular hypertrophy (LVH) as a contributor to SCD and therapeutic target in ESRD.

Etiology of Sudden Cardiac Death in ESRD

In experimental models, uremia inhibits compensatory angiogenesis in response to hypoxia⁶. Experimental CKD is characterized by decreased myocardial capillary density, reduced ischemia tolerance, and increased infarct size after coronary artery ligation⁶⁻¹¹. These changes are accompanied by LVH with accumulation of interstitial collagens and myocardial fibrosis that are at least partly independent of hypertension^{7-9, 12}. Although human data is more limited, similar changes have been observed in a few studies. In a classic study by Ritz and Amman, for example, ESRD patients with LVH (but without overt coronary disease) demonstrated myocyte hypertrophy, loss of myocardial capillaries, increased interstitial fibrosis, and a reduced capillary to myocyte ratio compared with patients with preserved renal function¹³.

Clinical surrogates for these myocardial changes are consistent with the experimental and pathologic studies. Myocardial coronary flow reserve—a measure of microvascular supply and function—declines in parallel with glomerular filtration¹⁴⁻¹⁷, while coronary collateral vessels—whose presence reduces the risk of death in CAD^{18, 19}—are 41% less abundant in individuals mild-moderate CKD than patients without CKD²⁰. Similarly Left ventricular (LV) mass (see below), diastolic function and late gadolinium enhancement (a marker of myocardial scar/fibrosis) increase dramatically as GFR declines and are associated with risk of death²¹⁻²⁸.

The combination of increased myocyte size, interstitial collagen content, and microvascular rarefaction increases intra-capillary distances and capillary to cardiomyocyte distances^{9, 13}. These changes inhibit basal diffusion of oxygen and glucose from capillary to myocyte and reduce ischemia tolerance thereby heightening the risk of myocyte necrosis when coronary blood flow is reduced. Increased myocyte size, interstitial fibrosis and larger distances between adjacent myocytes lead to concomitant disruption of myocardial electrical

pathways. The combination lowers the threshold for the propagation of fatal arrhythmias and is likely a key mechanism underlying the high incidence of SCD in dialysis-dependent ESRD. Thus, LVH with pathologic mismatching of myocyte to capillary supply stands out as critical and potentially modifiable risk factor for CV death in dialysis dependent ESRD.

Etiology of Left Ventricular Hypertrophy

Pressure overload—either from hypertension or decreased vascular compliance (e.g. from cardiac calcification)—is a major contributor to LVH in ESRD^{29, 30}. Increased preload, makes is similarly important, particularly to the development of eccentric rather than the concentric LVH which characterizes pure pressure overload^{29, 31}. Factors implicated in preload related LVH include anemia³², arterial-venous dialysis accesses with high output³³, and salt and volume overload^{34, 35} (a ubiquitous factor in thrice-weekly maintenance dialysis patients). Finally, numerous circulating and cellular factors—many of which are excessively active in the setting of ESRD—may independently contribute to the development of LVH or modify the associations of preload and afterload with LVH.

The renin-angiotensin-aldosterone system has been recognized as a crucial component in the development of LVH^{35, 36}, and clinical studies are consistent with an important role in the LVH of ESRD³⁷⁻⁴⁰. The role of the bone and mineral metabolism axis has been more recently recognized, but emerging evidence is generally consistent with important roles for vitamin D⁴¹, parathyroid hormone^{42, 43}, and FGF-23^{44, 45} in the adverse myocardial remodeling of ESRD. Finally, emerging evidence implicates a host of additional factors such as disordered nitric oxide metabolism^{46, 47}, elevated concentrations of endogenous cardiac glycosides⁴⁸, and changes in mammalian target of rapamycin (mTOR) pathway signalling⁴⁹, among other factors, as CKD-specific contributors to adverse cardiac remodeling (Figure 1).

Prevalence and Progression

LVH is highly prevalent in the dialysis population and was present in nearly 75% of 433 incident patients in a seminal study by Foley in 1995⁵⁰. Similarly, in a smaller study of incident Japanese dialysis patients 68% had LVH⁵¹. More recent analyses of the Chronic Renal Insufficiency Cohort and a Japanese inception cohort showed that 79% and 85% of individuals starting dialysis had LVH at the time of initiation^{52, 53}. LVH frequency is also high in prevalent dialysis patients but actually appears to be slightly less common. The incidence of LVH has varied across studies ranging between 36%- 77%⁵⁴⁻⁵⁸ in relatively unselected cohorts of prevalent dialysis patients, but is likely higher among truly unselected populations including individuals with known heart failure or CV disease.

The author is unaware of studies directly comparing the incidence of LVH in similarly defined populations of prevalent and incident hemodialysis patients. However, several studies have examined the progression of ventricular remodeling in the absence of anti-LVH therapy. In an observational study of 161 prevalent dialysis patients without congestive heart failure and with baseline ejection fraction >35%, there was a significant 6.7% increase of left ventricular mass index (LVMI) over an average 18 month interval between echocardiographic studies. Interestingly, although LVH increased on average, there was a

distinct association between baseline LVMI and LVH progression—individuals in the upper quartile of LVMI showed much smaller increases than those with more normal ventricular geometry at baseline⁵⁹. Conversely, in an older study of 227 PD and HD patients, LVMI decreased in up to 48% of patients between inception and 1-year while increasing or remaining stable in the remainder⁶⁰. Findings were similar in a study of 111 incident dialysis patients in Korea, 32 of whom had repeat echocardiography 6 months after an initial study. Although mean LVMI increased on average from 196 g/m² to 210 g/m² (P=0.05), it was stable or decreased in 41% of patients⁶¹.

More recently, in a clinical trial enrolling 596 anemic, relatively new (dialysis vintage < 18 months) HD patients without heart failure or ischemic heart disease, progressive LVH was observed regardless of randomized therapy⁶². LVMI increased from 114 g/m² at baseline to 121 g/m² at 24 weeks, 123 g/m² at 48 weeks and 128 g/m² at 96 weeks (P<0.001). Despite a mean increase in LVMI, LVH was stable or decreased in 37% of patients.

In summary, LVMI increases substantially in the majority of dialysis patients treated according to the usual standard of care. However, it is clear that an increase in LVMI is not inevitable. A substantial minority of dialysis patients do not experience LVH progression during medium to long-term follow-up, and a minority actually experience substantial LVH regression.

Association of Baseline LVH with Outcomes

It should be noted that the presence of either baseline or progressive LVH is strongly associated with adverse outcomes. It is likely that these studies actually underestimate the likelihood and degree of LVH progression in the dialysis population given a higher likelihood of early death (with subsequent failure to obtain follow-up evaluations of left ventricular structure) in those with the most severe or progressive LVH.

Associations of baseline LVH with survival have been well-studied. Higher LVMI is clearly a risk-factor for mortality, but whether this effect is independently associated with outcomes is less certain. A seminal study of 91 incident dialysis patients beginning therapy between 1983-1987 was one of the earliest to demonstrate an association between baseline LVH and all-cause or CV mortality with adjusted hazard ratios of 2.9 (95% CI: 1.3-6.7) and 2.7 (95% CI: 0.9-8.2), respectively⁶³. Similarly an analysis of 2257 individuals who initiated dialysis between 1996-1997 demonstrated a relative risk of 1.29 (95% CI: 1.07-1.56) for 2-year mortality after adjustment for demographic factors. The risk ratio remained >1.0 but lost significance with further adjustment for prevalent cardiovascular disease⁶⁴. Similarly in a study of 433 prevalent patients studied in the mid 1980s, higher LVMI at baseline was independently associated with significantly increased late (after 2-years) mortality. However, crude associations with overall mortality during the entire length of follow-up were attenuated in multi-variable models adjusted for demographics, diabetes and the presence of ischemic CV disease⁶⁵. In a similar vein, in the aforementioned clinical trial of 596 anemic hemodialysis patients⁶², an association of LVMI with combined CV events and death was present (HR 1.14, 95% CI: 1.10-1.29 for LVMI increments of 21 g/m²) in models

adjusting for age and sex, but the association was lost with further adjustment for comorbidities and cardiovascular biomarkers.

A few studies have demonstrated a fully independent association of LVH with all-cause or CV mortality. For example, a recent study of 317 incident patients showed that baseline LVH was associated with a >11-fold increase in the risk of CV death ($P=0.02$) after adjustment for baseline ejection fraction, age, diabetes, presence of coronary disease, and electrocardiographic parameters⁶⁶. An analysis of the randomized FOSODIAL trial (fosinopril vs. placebo for 24 months), similarly demonstrated an independent association between LVMI and the risk of subsequent CV events after correction for relevant comorbidities⁶⁷.

In contrast, a few studies have not found significant associations between LVH and survival. Madsen, studied 109 prevalent hemodialysis patients and found no association between LVH and mortality in either univariate or multi-variable analyses, although there were only 34 deaths during 2-years of follow-up⁵⁵. Similarly in a study by Satyan of 150 prevalent dialysis patients followed for 2 years (46 deaths), LVMI was not a predictor of mortality⁵⁴. The lack of an association in these studies may reflect the small sample size, limited number of fatalities, and correction for cardiac biomarkers whose concentration are likely to be correlated with LVMI and may be on the causal pathway between LVH and outcomes. However, a recently published study of 404 incident Japanese hemodialysis actually demonstrated that *lower* LVMI at baseline was associated with worse all-cause and CV survival in both crude and adjusted analyses. Interestingly, this “reverse epidemiology” was apparent only in patients without pre-dialysis erythropoietin use⁵³.

The meaning of these disparate findings is open to interpretation, but the majority of studies, particularly the better powered ones, have demonstrated strong associations between LVH/LVMI and survival/CV outcomes. Thus, it is reasonable to conclude that the presence of baseline LVH is a strong risk factor for adverse outcomes in dialysis patients. Whether this effect is independent of the association of LVH with other comorbidities such as diabetes, hypertension and duration of dialysis or reflects a direct causal effects, is an issue requiring further study.

LVH Progression and Outcomes

Relatively few studies have assessed associations of change in LVH with outcomes in individuals with ESRD. However, these few studies show consistently strong links between change in left ventricular mass and outcomes. In a seminal study, 227 prevalent dialysis patients underwent baseline echocardiography within 1 year of starting dialysis and repeat echocardiogram one year later. Increased LVMI was strongly associated *de novo* congestive heart failure in multivariable models—HR per 20 g/m² 1.3 (95% CI: 1.1-1.5)⁶⁰. In the CREED study, 173 prevalent dialysis patients without a history of congestive heart failure and ejection fraction >35% were observed with serial echocardiograms⁵⁹. There was graded relationship between the rate of increase in LVMI and the risk of death—adjusted HR 3.07 (95% CI: 1.34-7.05) for individuals with rates of LVMI increase above the 75th percentile compared to those below the 25th percentile. Similar associations were observed

in an analysis of fatal cardiovascular events. Finally, in a single-center prospective study of 153 incident and prevalent HD patients who underwent multi-factorial intervention of hypertension, anemia and volume overload, each 10% decrease in LVM was independently associated with a significant decrease in the risk of both all-cause (HR 0.78, 95 CI: 0.63-0.92) and CV mortality (HR 0.72, 95% CI: 0.51-0.90)⁶⁸.

Interventions to Regress LVH

As reviewed above, it is clear that progression of LVH is not inevitable, and that stability or progressive decreases in LVMI occur in a substantial proportion of dialysis patients. This high proportion makes it difficult to assess the efficacy of potential therapeutics for LVH on the basis of non-randomized studies. However, relatively few randomized trials have assessed LVH as a primary outcome measure. A full review of these studies is beyond the scope of this manuscript, but several studies strongly suggest the potential for a variety of interventions to mitigate progression or even reverse established LVH. A brief review of several illustrative studies is presented.

Angiotensin Blockade

A few trials have confirmed the potential of angiotensin blockade to improve LVH in ESRD. In a small trial, 30 chronic HD patients were randomized to losartan, enalapril or amlodipine. At 6 months, LVMI reduction was significantly lower with losartan (-24.7 +/- 3.2%) than with amlodipine (-10.5 +/- 5.2%) or enalapril (-11.2 +/- 4.1%) , despite similar blood pressure reduction⁶⁹. Although a better response with angiotensin blockers compared to converting enzymes was not observed in another small trial of 33 incident, diabetic hemodialysis patients randomized to enalapril 10 mg daily, losartan 100 mg daily or combination therapy, there was a blood pressure independent benefit of more complete angiotensin blockade. At 1 year, LVH progressively decreased in all 3 groups, but there was an additional 28% reduction in the dual therapy group ($P<0.05$)⁷⁰ despite similar blood pressure reduction. A 3rd small trial compared imadapril (2.5 mg daily) with placebo in 30 hemodialysis patients. Despite no significant impact on blood pressure in either group, LVMI was significantly decreased by 18% in the imidapril group but was unchanged in the placebo group ($P<0.05$)⁷¹. Although these studies are small, in total they provide intriguing evidence supporting the potential for angiotensin blockade to regress LVH. Large studies seem warranted on this basis. However, the failure of fosinopril to improve all-cause or CV mortality in a relatively sizeable outcomes trial limits enthusiasm and raises questions about whether the improvement in LV morphology will necessarily translate into better clinical outcomes.⁷².

Dialysis Frequency

In the Frequent Hemodialysis Network Daily Trial, 245 patients were randomized to 6x/week or 3x/week HD. A nocturnal trial randomized 87 patients to long nocturnal (3x/week) vs. conventional dialysis. Cardiac MRI was performed at baseline and 12 months. LVMI decreased with intervention compared to control in both the daily (-13.1g, 95% CI: -5.0, -21.3) and nocturnal trials (-10.1g, 95% CI: -23.7, 1.8) but the difference achieved significance only in larger, daily trial⁷³. These data demonstrate a clear effect of more

frequent dialysis on LVH but leave uncertain whether more frequent dialysis achieves this impact through improved clearance, better control of volume and hypertension or through other, unrecognized mechanisms.

Anemia Management

Multiple studies have examined the impact of exogenous erythropoietin on LVH but few have been randomized. Although a meta-analysis of both randomized and cohort studies suggested a significant impact on LVH in dialysis patients with severe anemia at baseline this effect was observed principally in cohort studies and was not observed in randomized trials⁷⁴. In the largest randomized studies including 596⁶² and 146⁷⁵ hemodialysis patients with moderate anemia, correction to a higher hemoglobin had no significant impact on LVMI. Thus, available data have failed to demonstrate a convincing impact of anemia correction on ventricular geometry despite non-randomized studies suggesting strong associations of anemia or anemia correction and LVH.

Conclusions

Biologic considerations suggest that multiple pathways contribute to development of LVH in ESRD and that LVH is an important mechanism underlying sudden death in dialysis dependent ESRD. It is highly prevalent, frequently progressive, and is clearly a risk factor for CV events and death in this population. Additionally, several trials have demonstrated the potential to modify LVH in dialysis-dependent ESRD using readily available tools or by interfering with well understood physiologic pathways. These considerations demonstrate that LVH is clearly a modifiable risk factor in ESRD.

However, a more appropriate question is whether targeting LVH is now warranted. The answer to this question is less certain. Despite promising results, few trials, mostly of modest size, have targeted LVH in ESRD. Important questions remain about the ideal therapies for LVH and optimal populations for their application. It remains uncertain whether LVH is an independent risk factor in ESRD or whether the association primarily reflects the association of LVH with prevalent conditions such as hypertension and volume overload--in which case these factors might be the better targets. Additionally, associations of LVH improvement with clinical outcomes have not been widely studied. Whether therapeutic improvement in LVMI will reduce mortality and whether that improvement will be equivalent for similar degrees of LVMI change across therapies with divergent mechanisms of action is unknown (additional considerations in Table 1). Given these considerations LVH improvement cannot yet be considered a reliable surrogate outcome measure for use in the context of ESRD.

In summary, LVH is a promising target and the weight of evidence suggests that it is a modifiable risk factor in ESRD and that targeting LVH reduction may ultimately become the standard of care in ESRD. Nevertheless, at this time randomized, controlled studies are warranted to better define the optimal therapeutic approach to LVH and its suitability as a surrogate outcome measure before a clinical focus on LVH reduction can be widely advocated.

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References and Recommended Reading

1. U.S. Renal Data System. USRDS 2013 Annual Data Report: Atlas of End-Stage Renal Disease in the United States. 2013
2. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, Wanner C, Krane V, Cass A, Craig J, Neal B, Jiang L, Hooi LS, Levin A, Agodoa L, Gaziano M, Kasiske B, Walker R, Massy ZA, Feldt-Rasmussen B, Krairittichai U, Ophascharoensuk V, Fellstrom B, Holdaas H, Tesar V, Wiecek A, Grobbee D, de Zeeuw D, Gronhagen-Riska C, Dasgupta T, Lewis D, Herrington W, Mafham M, Majoni W, Wallendszus K, Grimm R, Pedersen T, Tobert J, Armitage J, Baxter A, Bray C, Chen Y, Chen Z, Hill M, Knott C, Parish S, Simpson D, Sleight P, Young A, Collins R. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet*. 2011; 377:2181–92. [PubMed: 21663949]
3. Wanner C, Krane V, Marz W, Olschewski M, Mann JF, Ruf G, Ritz E. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med*. 2005; 353:238–48. [PubMed: 16034009]
4. Fellstrom BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, Chae DW, Chevaile A, Cobbe SM, Gronhagen-Riska C, De Lima JJ, Lins R, Mayer G, McMahon AW, Parving HH, Remuzzi G, Samuelsson O, Sonkodi S, Sci D, Suleymanlar G, Tsakiris D, Tesar V, Todorov V, Wiecek A, Wuthrich RP, Gottlow M, Johnsson E, Zannad F. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *N Engl J Med*. 2009; 360:1395–407. [PubMed: 19332456]
5. Himmelfarb J, Stenvinkel P, Ikizler TA, Hakim RM. The elephant in uremia: oxidant stress as a unifying concept of cardiovascular disease in uremia. *Kidney Int*. 2002; 62:1524–38. [PubMed: 12371953]
6. Jacobi J, Porst M, Cordasic N, Namer B, Schmieder RE, Eckardt KU, Hilgers KF. Subtotal nephrectomy impairs ischemia-induced angiogenesis and hindlimb re-perfusion in rats. *Kidney Int*. 2006; 69:2013–21. [PubMed: 16641920]
7. Amann K, Hofstetter J, Campean V, Koch A, Gross ML, Veelken R, Ritz E. Nonhypotensive dose of beta-adrenergic blocker ameliorates capillary deficits in the hearts of rats with moderate renal failure. *Virchows Arch*. 2006
8. Amann K, Neimeier KA, Schwarz U, Tornig J, Matthias S, Orth SR, Mall G, Ritz E. Rats with moderate renal failure show capillary deficit in heart but not skeletal muscle. *Am J Kidney Dis*. 1997; 30:382–8. [PubMed: 9292567]
9. Amann K, Wiest G, Zimmer G, Gretz N, Ritz E, Mall G. Reduced capillary density in the myocardium of uremic rats--a stereological study. *Kidney Int*. 1992; 42:1079–85. [PubMed: 1453595]
10. Dikow R, Kihm LP, Zeier M, Kapitzka J, Tornig J, Amann K, Tiefenbacher C, Ritz E. Increased infarct size in uremic rats: reduced ischemia tolerance? *J Am Soc Nephrol*. 2004; 15:1530–6. [PubMed: 15153563]
11. Tyralla K, Amann K. Morphology of the heart and arteries in renal failure. *Kidney Int Suppl*. 2003:S80–3. [PubMed: 12694316]
12. Dikow R, Schmidt U, Kihm LP, Schaier M, Schwenger V, Gross ML, Katus HA, Zeier M, Hardt SE. Uremia aggravates left ventricular remodeling after myocardial infarction. *Am J Nephrol*. 2010; 32:13–22. [PubMed: 20484895]
13. Amann K, Breitbach M, Ritz E, Mall G. Myocyte/capillary mismatch in the heart of uremic patients. *J Am Soc Nephrol*. 1998; 9:1018–22. [PubMed: 9621284]

14. Chade AR, Brosh D, Higano ST, Lennon RJ, Lerman LO, Lerman A. Mild renal insufficiency is associated with reduced coronary flow in patients with non-obstructive coronary artery disease. *Kidney Int.* 2006; 69:266–71. [PubMed: 16408115]
15. Koivuvuori N, Tertti R, Jarvisalo M, Pietila M, Hannukainen J, Sundell J, Nuutila P, Knuuti J, Metsarinne K. Increased basal myocardial perfusion in patients with chronic kidney disease without symptomatic coronary artery disease. *Nephrol Dial Transplant.* 2009; 24:2773–9. [PubMed: 19369689]
16. Tok D, Gullu H, Erdogan D, Topcu S, Ciftci O, Yildirim I, Muderrisoglu H. Impaired coronary flow reserve in hemodialysis patients: a transthoracic Doppler echocardiographic study. *Nephron Clin Pract.* 2005; 101:c200–6. [PubMed: 16113583]
17. Charytan DM, Shelbert HR, Di Carli MF. Coronary microvascular function in early chronic kidney disease. *Circ Cardiovasc Imaging.* 2011; 3:663–71. [PubMed: 20851872]
18. Meier P, Gloekler S, Zbinden R, Beckh S, de Marchi SF, Zbinden S, Wustmann K, Billinger M, Vogel R, Cook S, Wenaweser P, Togni M, Windecker S, Meier B, Seiler C. Beneficial effect of recruitable collaterals: a 10-year follow-up study in patients with stable coronary artery disease undergoing quantitative collateral measurements. *Circulation.* 2007; 116:975–83. [PubMed: 17679611]
19. Sabia PJ, Powers ER, Ragosta M, Sarembock IJ, Burwell LR, Kaul S. An association between collateral blood flow and myocardial viability in patients with recent myocardial infarction. *N Engl J Med.* 1992; 327:1825–31. [PubMed: 1448120]
20. Sezer M, Ozcan M, Okcular I, Elitok A, Umman S, Umman B, Tayyareci Y, Olcay A, Nisanci Y, Bilge AK, Meric M. A potential evidence to explain the reason behind the devastating prognosis of coronary artery disease in uraemic patients: Renal insufficiency is associated with poor coronary collateral vessel development. *Int J Cardiol.* 2006
21. Mark PB, Johnston N, Groenning BA, Foster JE, Blyth KG, Martin TN, Steedman T, Dargie HJ, Jardine AG. Redefinition of uremic cardiomyopathy by contrast-enhanced cardiac magnetic resonance imaging. *Kidney Int.* 2006; 69:1839–45. [PubMed: 16508657]
22. Foley RN, Curtis BM, Randell EW, Parfrey PS. Left ventricular hypertrophy in new hemodialysis patients without symptomatic cardiac disease. *Clin J Am Soc Nephrol.* 5:805–13. [PubMed: 20378644]
23. de Almeida EA, de Oliveira EI, Lopes JA, Almeida AG, Lopes MG, Prata MM. Diastolic function in several stages of chronic kidney disease in patients with autosomal dominant polycystic kidney disease: a tissue Doppler imaging study. *Kidney Blood Press Res.* 2007; 30:234–9. [PubMed: 17575469]
24. Afshinnia F, Spitalewitz S, Chou SY, Gunsburg DZ, Chadow HL. Left ventricular geometry and renal function in hypertensive patients with diastolic heart failure. *Am J Kidney Dis.* 2007; 49:227–36. [PubMed: 17261425]
25. Edwards NC, Ferro CJ, Townend JN, Steeds RP. Aortic distensibility and arterial-ventricular coupling in early chronic kidney disease: a pattern resembling heart failure with preserved ejection fraction. *Heart.* 2008; 94:1038–43. [PubMed: 18308865]
26. Masugata H, Senda S, Goda F, Yamagami A, Okuyama H, Kohno T, Hosomi N, Yukiiri K, Noma T, Imai M, Kiyomoto H, Nishiyama A, Kohno M. Echocardiographic assessment of the cardio-renal connection: is left ventricular hypertrophy or diastolic function more closely correlated with estimated glomerular filtration rate in patients with cardiovascular risk factors? *Clin Exp Hypertens.* 2010; 32:113–20. [PubMed: 20374184]
27. Bruch C, Rothenburger M, Gotzmann M, Wichter T, Scheld HH, Breithardt G, Gradaus R. Chronic kidney disease in patients with chronic heart failure--impact on intracardiac conduction, diastolic function and prognosis. *Int J Cardiol.* 2007; 118:375–80. [PubMed: 17049387]
28. Wang AY, Wang M, Lam CW, Chan IH, Zhang Y, Sanderson JE. Left ventricular filling pressure by Doppler echocardiography in patients with end-stage renal disease. *Hypertension.* 2008; 52:107–14. [PubMed: 18474835]
29. Gross ML, Ritz E. Hypertrophy and fibrosis in the cardiomyopathy of uremia--beyond coronary heart disease. *Semin Dial.* 2008; 21:308–18. [PubMed: 18627569]

30. Nitta K, Akiba T, Uchida K, Otsubo S, Otsubo Y, Takei T, Ogawa T, Yumura W, Kabaya T, Nihei H. Left ventricular hypertrophy is associated with arterial stiffness and vascular calcification in hemodialysis patients. *Hypertens Res.* 2004; 27:47–52. [PubMed: 15055255]
31. Glasscock RJ, Pecoits-Filho R, Barberato SH. Left ventricular mass in chronic kidney disease and ESRD. *Clin J Am Soc Nephrol.* 2009; 4(Suppl 1):S79–91. [PubMed: 19996010]
32. Naito Y, Tsujino T, Matsumoto M, Sakoda T, Ohyanagi M, Masuyama T. Adaptive response of the heart to long-term anemia induced by iron deficiency. *Am J Physiol Heart Circ Physiol.* 2009; 296:H585–93. [PubMed: 19136608]
33. MacRae JM. Vascular access and cardiac disease: is there a relationship? *Curr Opin Nephrol Hypertens.* 2006; 15:577–82. [PubMed: 17053470]
34. Ozkahya M, Ok E, Cirit M, Aydin S, Akcicek F, Basci A, Dorhout Mees EJ. Regression of left ventricular hypertrophy in haemodialysis patients by ultrafiltration and reduced salt intake without antihypertensive drugs. *Nephrol Dial Transplant.* 1998; 13:1489–93. [PubMed: 9641180]
35. Yamakawa H, Imamura T, Matsuo T, Onitsuka H, Tsumori Y, Kato J, Kitamura K, Koikawa Y, Eto T. Diastolic wall stress and ANG II in cardiac hypertrophy and gene expression induced by volume overload. *Am J Physiol Heart Circ Physiol.* 2000; 279:H2939–46. [PubMed: 11087250]
36. Paulis L, Matuskova J, Adamcova M, Pelouch V, Simko J, Krajcovicova K, Potacova A, Hulin I, Janega P, Pechanova O, Simko F. Regression of left ventricular hypertrophy and aortic remodelling in NO-deficient hypertensive rats: effect of L-arginine and spironolactone. *Acta Physiol (Oxf).* 2008; 194:45–55. [PubMed: 18419778]
37. Sato A, Funder JW, Saruta T. Involvement of aldosterone in left ventricular hypertrophy of patients with end-stage renal failure treated with hemodialysis. *Am J Hypertens.* 1999; 12:867–73. [PubMed: 10509543]
38. Steigerwalt S, Zafar A, Mesiha N, Gardin J, Provenzano R. Role of aldosterone in left ventricular hypertrophy among African-American patients with end-stage renal disease on hemodialysis. *Am J Nephrol.* 2007; 27:159–63. [PubMed: 17317951]
39. Cannella G, Paoletti E, Delfino R, Peloso G, Rolla D, Molinari S. Prolonged therapy with ACE inhibitors induces a regression of left ventricular hypertrophy of dialyzed uremic patients independently from hypotensive effects. *Am J Kidney Dis.* 1997; 30:659–64. [PubMed: 9370181]
40. Mitsuhashi H, Tamura K, Yamauchi J, Ozawa M, Yanagi M, Dejima T, Wakui H, Masuda S, Azuma K, Kanaoka T, Ohsawa M, Maeda A, Tsurumi-Ikeya Y, Okano Y, Ishigami T, Toya Y, Tokita Y, Ohnishi T, Umemura S. Effect of losartan on ambulatory short-term blood pressure variability and cardiovascular remodeling in hypertensive patients on hemodialysis. *Atherosclerosis.* 2009; 207:186–90. [PubMed: 19423110]
41. Mizobuchi M, Nakamura H, Tokumoto M, Finch J, Morrissey J, Liapis H, Slatopolsky E. Myocardial effects of VDR activators in renal failure. *J Steroid Biochem Mol Biol.* 2010; 121:188–92. [PubMed: 20236614]
42. Fujii H, Kim JI, Abe T, Umezu M, Fukagawa M. Relationship between parathyroid hormone and cardiac abnormalities in chronic dialysis patients. *Internal medicine.* 2007; 46:1507–12. [PubMed: 17878635]
43. van Ballegooijen AJ, Visser M, Kestenbaum B, Siscovick DS, de Boer IH, Gottdiener JS, deFilippi CR, Brouwer IA. Relation of vitamin D and parathyroid hormone to cardiac biomarkers and to left ventricular mass (from the Cardiovascular Health Study). *Am J Cardiol.* 2013; 111:418–24. [PubMed: 23168286]
44. Faul C, Amaral AP, Oskouei B, Hu MC, Sloan A, Isakova T, Gutierrez OM, Aguillon-Prada R, Lincoln J, Hare JM, Mundel P, Morales A, Scialla J, Fischer M, Soliman EZ, Chen J, Go AS, Rosas SE, Nessel L, Townsend RR, Feldman HI, St John Sutton M, Ojo A, Gadegbeku C, Di Marco GS, Reuter S, Kentrup D, Tiemann K, Brand M, Hill JA, Moe OW, Kuro OM, Kusek JW, Keane MG, Wolf M. FGF23 induces left ventricular hypertrophy. *J Clin Invest.* 2011; 121:4393–408. [PubMed: 21985788]
45. Gutierrez OM, Januzzi JL, Isakova T, Laliberte K, Smith K, Collerone G, Sarwar A, Hoffmann U, Coglianese E, Christenson R, Wang TJ, deFilippi C, Wolf M. Fibroblast growth factor 23 and left ventricular hypertrophy in chronic kidney disease. *Circulation.* 2009; 119:2545–52. [PubMed: 19414634]

46. Kazakov A, Muller P, Jagoda P, Semenov A, Bohm M, Laufs U. Endothelial nitric oxide synthase of the bone marrow regulates myocardial hypertrophy, fibrosis, and angiogenesis. *Cardiovasc Res.* 2012; 93:397–405. [PubMed: 22106415]
47. Zoccali C, Mallamaci F, Maas R, Benedetto FA, Tripepi G, Malatino LS, Cataliotti A, Bellanuova I, Boger R. Left ventricular hypertrophy, cardiac remodeling and asymmetric dimethylarginine (ADMA) in hemodialysis patients. *Kidney Int.* 2002; 62:339–45. [PubMed: 12081596]
48. Kennedy DJ, Vetteth S, Periyasamy SM, Kanj M, Fedorova L, Khouri S, Kahaleh MB, Xie Z, Malhotra D, Kolodkin NI, Lakatta EG, Fedorova OV, Bagrov AY, Shapiro JI. Central role for the cardiotonic steroid marinobufagenin in the pathogenesis of experimental uremic cardiomyopathy. *Hypertension.* 2006; 47:488–95. [PubMed: 16446397]
49. Siedlecki AM, Jin X, Muslin AJ. Uremic cardiac hypertrophy is reversed by rapamycin but not by lowering of blood pressure. *Kidney Int.* 2009; 75:800–8. [PubMed: 19165175]
50. Foley RN, Parfrey PS, Harnett JD, Kent GM, Martin CJ, Murray DC, Barre PE. Clinical and echocardiographic disease in patients starting end-stage renal disease therapy. *Kidney Int.* 1995; 47:186–92. [PubMed: 7731145]
51. Takeda A, Toda T, Iwamoto H, Watanabe K, Matsui N. Long-term evolution and changing associations of left ventricular hypertrophy after starting hemodialysis. *Nephron Clin Pract.* 2008; 110:c126–32. [PubMed: 18931516]
52. Bansal N, Keane M, Delafontaine P, Dries D, Foster E, Gadegbeku CA, Go AS, Hamm LL, Kusek JW, Ojo AO, Rahman M, Tao K, Wright JT, Xie D, Hsu CY, Investigators CS. A longitudinal study of left ventricular function and structure from CKD to ESRD: the CRIC study. *Clin J Am Soc Nephrol.* 2013; 8:355–62. This analysis of the CRIC study gives detailed information on longitudinal change in myocardial anatomy as individuals progress from CKD to ESRD. [PubMed: 23411431]
53. Hayashi T, Kimura T, Yasuda K, Obi Y, Sasaki K, Iio K, Miyasato K, Kamimura T, Kitamura H, Tsubakihara Y, Rakugi H, Isaka Y. Prognostic significance of left ventricular hypertrophy observed at dialysis initiation depends on the pre-dialysis use of erythropoiesis-stimulating agents. *Clinical and experimental nephrology.* 2013; 17:294–303. Intriguing paper demonstrating inverse associations between baseline LVH and outcomes in a large, Japanese cohort. [PubMed: 23100176]
54. Satyan S, Light RP, Agarwal R. Relationships of N-terminal pro-B-natriuretic peptide and cardiac troponin T to left ventricular mass and function and mortality in asymptomatic hemodialysis patients. *Am J Kidney Dis.* 2007; 50:1009–19. [PubMed: 18037101]
55. Madsen LH, Ladefoged S, Corell P, Schou M, Hildebrandt PR, Atar D. N-terminal pro brain natriuretic peptide predicts mortality in patients with end-stage renal disease in hemodialysis. *Kidney Int.* 2007; 71:548–54. [PubMed: 17299526]
56. Dimitrijevic Z, Cvetkovic T, Stojanovic M, Paunovic K, Djordjevic V. Prevalence and risk factors of myocardial remodeling in hemodialysis patients. *Ren Fail.* 2009; 31:662–7. [PubMed: 19817519]
57. Virga G, Stomaci B, Munaro A, Mastrosimone S, Cara M, Artuso E, Piovesana P. Systolic and diastolic function in renal replacement therapy: a cross-sectional study. *J Nephrol.* 2006; 19:155–60. [PubMed: 16736413]
58. Kutlay S, Dincer I, Sengul S, Nergizoglu G, Duman N, Erturk S. The long-term behavior and predictors of left ventricular hypertrophy in hemodialysis patients. *Am J Kidney Dis.* 2006; 47:485–92. [PubMed: 16490628]
59. Zoccali C, Benedetto FA, Mallamaci F, Tripepi G, Giaccone G, Stancanelli B, Cataliotti A, Malatino LS. Left ventricular mass monitoring in the follow-up of dialysis patients: prognostic value of left ventricular hypertrophy progression. *Kidney Int.* 2004; 65:1492–8. [PubMed: 15086493]
60. Foley RN, Parfrey PS, Kent GM, Harnett JD, Murray DC, Barre PE. Serial change in echocardiographic parameters and cardiac failure in end-stage renal disease. *J Am Soc Nephrol.* 2000; 11:912–6. [PubMed: 10770969]
61. Moon KH, Song IS, Yang WS, Shin YT, Kim SB, Song JK, Park JS. Hypoalbuminemia as a risk factor for progressive left-ventricular hypertrophy in hemodialysis patients. *Am J Nephrol.* 2000; 20:396–401. [PubMed: 11092998]

62. Foley RN, Curtis BM, Randell EW, Parfrey PS. Left ventricular hypertrophy in new hemodialysis patients without symptomatic cardiac disease. *Clin J Am Soc Nephrol.* 2010; 5:805–13. [PubMed: 20378644]
63. Silberberg JS, Barre PE, Prichard SS, Sniderman AD. Impact of left ventricular hypertrophy on survival in end-stage renal disease. *Kidney Int.* 1989; 36:286–90. [PubMed: 2528654]
64. Stack AG, Saran R. Clinical correlates and mortality impact of left ventricular hypertrophy among new ESRD patients in the United States. *Am J Kidney Dis.* 2002; 40:1202–10. [PubMed: 12460039]
65. Foley RN, Parfrey PS, Harnett JD, Kent GM, Murray DC, Barre PE. The prognostic importance of left ventricular geometry in uremic cardiomyopathy. *J Am Soc Nephrol.* 1995; 5:2024–31. [PubMed: 7579050]
66. Kim SJ, Oh HJ, Yoo DE, Shin DH, Lee MJ, Kim HR, Park JT, Han SH, Yoo TH, Choi KH, Kang SW. Electrocardiographic left ventricular hypertrophy and outcome in hemodialysis patients. *PloS one.* 2012; 7:e35534. [PubMed: 22530043]
67. Kessler M, Zannad F, Leher P, Grunfeld JP, Thuilliez C, Leizorovicz A, Lechat P, Investigators F. Predictors of cardiovascular events in patients with end-stage renal disease: an analysis from the Fosinopril in dialysis study. *Nephrol Dial Transplant.* 2007; 22:3573–9. [PubMed: 17611249]
68. London GM, Pannier B, Guerin AP, Blacher J, Marchais SJ, Darne B, Metivier F, Adda H, Safar ME. Alterations of left ventricular hypertrophy in and survival of patients receiving hemodialysis: follow-up of an interventional study. *J Am Soc Nephrol.* 2001; 12:2759–67. [PubMed: 11729246]
69. Shibasaki Y, Masaki H, Nishiue T, Nishikawa M, Matsubara H, Iwasaka T. Angiotensin II type 1 receptor antagonist, losartan, causes regression of left ventricular hypertrophy in end-stage renal disease. *Nephron.* 2002; 90:256–61. [PubMed: 11867945]
70. Suzuki H, Kanno Y, Kaneko K, Kaneko M, Kotaki S, Mimura T, Takane H. Comparison of the effects of angiotensin receptor antagonist, angiotensin converting enzyme inhibitor, and their combination on regression of left ventricular hypertrophy of diabetes type 2 patients on recent onset hemodialysis therapy. *Therapeutic apheresis and dialysis : official peer-reviewed journal of the International Society for Apheresis, the Japanese Society for Apheresis, the Japanese Society for Dialysis Therapy.* 2004; 8:320–7.
71. Matsumoto N, Ishimitsu T, Okamura A, Seta H, Takahashi M, Matsuoka H. Effects of imidapril on left ventricular mass in chronic hemodialysis patients. *Hypertens Res.* 2006; 29:253–60. [PubMed: 16778332]
72. Zannad F, Kessler M, Leher P, Grunfeld JP, Thuilliez C, Leizorovicz A, Lechat P. Prevention of cardiovascular events in end-stage renal disease: results of a randomized trial of fosinopril and implications for future studies. *Kidney Int.* 2006; 70:1318–24. [PubMed: 16871247]
73. Chan CT, Greene T, Chertow GM, Kliger AS, Stokes JB, Beck GJ, Daugirdas JT, Kotanko P, Larive B, Levin NW, Mehta RL, Rocco M, Sanz J, Yang PC, Rajagopalan S. Frequent Hemodialysis Network Trial G. Effects of frequent hemodialysis on ventricular volumes and left ventricular remodeling. *Clin J Am Soc Nephrol.* 2013; 8:2106–16. Randomized trial demonstrating dramatic improvement in LVMI with frequent hemodialysis compared to standard therapy. [PubMed: 23970131]
74. Parfrey PS, Lauve M, Latremouille-Viau D, Lefebvre P. Erythropoietin therapy and left ventricular mass index in CKD and ESRD patients: a meta-analysis. *Clin J Am Soc Nephrol.* 2009; 4:755–62. [PubMed: 19339417]
75. Foley RN, Parfrey PS, Morgan J, Barre PE, Campbell P, Cartier P, Coyle D, Fine A, Handa P, Kingma I, Lau CY, Levin A, Mendelssohn D, Muirhead N, Murphy B, Plante RK, Posen G, Wells GA. Effect of hemoglobin levels in hemodialysis patients with asymptomatic cardiomyopathy. *Kidney Int.* 2000; 58:1325–35. [PubMed: 10972697]

Abbreviations

LVH	left ventricular hypertrophy
LVMI	left ventricular mass index

CVD	cardiovascular disease
HD	hemodialysis
PD	peritoneal dialysis
HR	hazard ratio
CI	confidence interval

Key Points

- LVH is highly prevalent in individuals with ESRD
- LVH is a risk factor for death in the ESRD population but may not be independently associated with outcomes.
- Change in LVH over time is strongly associated with the risk of death during follow-up
- Therapeutic trials have confirmed the feasibility of LVH regression but have not confirmed an association of change with improvement in survival
- Additional evidence is needed before LVH reduction can be advocated as the standard of care

Figure 1. Contributors to Adverse Remodeling of the Left Ventricle in ESRD

Factors contributing to capillary dropout and left ventricular hypertrophy in ESRD. HTN-hypertension. LVH-left ventricular hypertrophy. ADMA-asymmetric dimethyl arginine. FGF-23-fibroblast growth factor 23. mTOR-mammalian target of rapamycin.

Table 1

Considerations for LVH as a Therapeutic Target in ESRD	
Pro	
High prevalence	
Strong (univariate) associates of baseline LVH with all-cause mortality and CV events	
Independent associations of LVMI progression with survival	
Treatable risk factor—demonstrated reversibility in randomized angiotensin blockade studies and frequent dialysis studies	
Multiple underlying pathways provide multiple targets for therapeutic intervention	
Easy to measure-echocardiography is non-invasive and widely available	
Con	
Uncertain whether an independent/causal risk factor	
LVH not established as a reliable surrogate outcome measure in ESRD—studies demonstrating associations of randomized change in LVMI with outcomes are lacking	
Optimal therapeutic maneuvers and targets (e.g. goal blood pressure) undefined	
Volume dependence of LVH measurement ³¹ —optimal timing of LVH relative to dialytic schedule uncertain	
Ideal interval between repeated assessments undefined	

LVH-left ventricular hypertrophy. LVMI-left ventricular mass index. CV-cardiovascular