IDEAL Cardiac Substudy – Final version 27/01/2012

Effect of early initiation of dialysis on cardiac structure and function: results from the echo sub-study of the IDEAL Trial

Short Title: Cardiac sub-study of the IDEAL renal dialysis trial

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ABSTRACT

Background: Abnormalities of cardiac structure and function are common in dialysis patients and cardiovascular disease (CVD) is the major cause of mortality in this group. Heart failure is a common clinical manifestation of CVD and is preceded by left ventricular hypertrophy (LVH) and There are variable reports about the impact of dialysis on LVH, both deleterious and beneficial. Our study investigated whether the timing of the initiation of dialysis impacted upon cardiac structure and function.

Study Design: Randomized controlled trial.

Setting & Participants: This is a cardiac sub-study involving 182 patients with stage V chronic kidney disease (CKD) in the IDEAL (Initiating Dialysis Early and Late) trial.

Intervention: The IDEAL trial randomized patients on the basis of estimated glomerular filtration rate (eGFR) calculated using the Cockcroft-Gault equation to commence dialysis early (GFR of 10-14 mL/min/1.73m^2), with the remainder starting late (5-7 mL/min/1.73m^2).

Outcomes & Measurements: Echocardiograms were performed at baseline and 12 months after randomization. The primary outcomes were the change in left ventricular mass indexed for height (LVMi) between baseline and at 12 months, LV ejection fraction (LVEF), systolic LV systolic annular velocity (Sa), ratio of mitral inflow velocity (E) to mitral annular velocity (Ea) (E/Ea) and left atrial volume/height (LAVi).

Results: LVMi at baseline was elevated but similar in both groups, with no significant change within or between groups at 12 months. E/Ea and LAVi were increased at baseline consistent with significant diastolic dysfunction; there were no differences between groups at 12 months, nor were any changes observed for left ventricular volumes, ejection fraction, stroke volume, and other echocardiographic parameters.

Limitations: Small multi-center study using echocardiography

Conclusion: Advanced cardiac disease in these patients with stage V chronic kidney disease did not progress over the 12 month study period, nor did planned early initiation of dialysis result in differences in any echocardiographic variables of cardiac structure and function.

Index words: dialysis, left ventricular hypertrophy, cardiovascular, IDEAL

INTRODUCTION

The association between chronic kidney disease (CKD) and cardiovascular disease (CVD) is well known: CVD is the major cause of death in these patients,[1] often mediated by arrhythmias, sudden cardiac death and heart failure (HF), and is commonly preceded by structural heart disease, such as left ventricular hypertrophy (LVH).[2] LVH, an important prognostic predictor in CKD patients[3,4], is associated with myocardial fibrosis[5] and diastolic dysfunction, leading to systolic dysfunction, and ultimately HF.[6] Dialysis-mediated LVH regression could potentially ameliorate the negative prognostic impact of LVH in patients with CKD. However, the impact of dialysis on LVH is uncertain - some studies report regression of LVH[7] with dialysis, but others report no impact[8,9] or even LVH progression.[10] Many of these studies were small and uncontrolled and thus subject to important bias and very few studies have reported other cardiac echocardiographic endpoints. Consequently, the true impact of initiating dialysis on cardiac structure and function remains uncertain.

The Initiating Dialysis Early and Late (IDEAL) study[11] was designed to determine whether early commencement of either peritoneal or hemodialysis, in people with stage V CKD reduced all-cause mortality in a randomized control trial, and offered a unique opportunity to study the impact of dialysis upon cardiovascular structure. We hypothesized that there could be differences in the progression of LVH and subsequently systolic and diastolic function (specifically slower progression with early-start dialysis) prehaps related to the initiation of dialysis. Thus, the aim of this mechanistic sub-study was to examine the impact of early initiation of dialysis on echocardiographic measures of cardiac structure and function within the confines of the IDEAL randomized controlled trial. If dialysis does regress LVH, this may offset the neutral impact of early dialysis upon prognosis demonstrated in the IDEAL trial.[12]

METHODS

Study Design

This is a sub-study of the IDEAL study, a randomized clinical trial that has been described previously.[11] Briefly, 32 centers in Australia and New Zealand recruited patients with progressive CKD and an estimated GFR (eGFR) between 10 and 15 mL/min/1.73m^2, which was determined using the Cockcroft-Gault equation, and corrected for body surface area. The main IDEAL trial randomized 828 adult patients to two groups: early or late initiation of renal dialysis, with a median time to dialysis of 1.8 months (95%CI 1.60, 2.23) and 7.4 months (95%CI 6.23, 8.27) respectively. During a median follow-up time of 3.59 years, 152(37.6%) patients in the early-start group died compared with 155 (36.6%) in the late-start group: (hazard ratio 1.04 (95%CI 0.83, 1.30) P=0.75) and there was no significant difference in adverse event rates between the groups. Thus the IDEAL study reported no difference in survival or clinical outcomes between the two randomized groups.[12] The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, the Good Clinical Practice guidelines of the International Conference of Harmonization, and local regulatory bodies and followed the CONSORT guidelines for clinical trials.

Setting and Participants

The cardiac sub-study was an elective sub-study. Patients were excluded from the IDEAL trial if they: were <18 years; had an eGFR<10 mL/min/1.73m^2, had live donor transplant planned within the next 12 months, had a recent malignancy that was likely to impact on survival, or were unable to provide written informed consent. Potential echo sub-study sites were identified from the participating hospitals on the basis of accessible high-quality digital echocardiographic facilities and resulted in 14 centers recruiting patients across New Zealand and Australia. The principal investigators of the IDEAL Trial were contacted to determine interest and a cardiology-based principal investigator was identified at each potential sub-study site. Additional and separate ethical approval was obtained, and all patients provided additional written informed consent, for the echocardiography sub-study.

Patients were randomized either to commence dialysis at an eGFR of 10-14 mL/min/1.73m^2 or to continue routine medical care and commence dialysis at an eGFR of 5-7 mL/min/1.73m^2. The study protocol allowed for patients allocated to the late-start arm to commence dialysis with an eGFR of greater than 7 mL/min/1.73m^2, based on the recommendation of their physician. Randomization was performed centrally by a computer-based service (Clinical Trials Research Unit (CTRU), University of Auckland, New Zealand) using a permuted block design stratified by: center; planned dialysis modality (hemodialysis or peritoneal dialysis); and the presence or absence of diabetes mellitus. Although planned dialysis modality was specified prior to randomization, the dialysis modality and regimen ultimately prescribed remained the choice of the patient and treating physician.

Outcomes and Measurements

Echocardiography Protocol

A collaborative sub-study group was developed, which included nephrologists and echocardiographers from each participating hospital, and a steering committee developed the protocol for data collection and image analysis. Two core echocardiography laboratories were established (at the Universities of Auckland and Queensland). To participate in this sub-study, echocardiography laboratories were required to be: experienced in research echocardiography; and have access to DICOM or RAW digital storage facilities. A detailed image acquisition protocol was developed and each site received one-to-one training from a research sonographer from the core laboratory. During the study, detailed feedback regarding image quality was provided to each site as required in order to maintain quality. Wherever possible the same equipment and sonographers were used at each site and all personnel were blind to clinical data and randomization group allocation at the time of echocardiography. Digital images were acquired and stored on optical disc/CD, with videotape backup if available. Echocardiography was performed at baseline (at the time of randomization) and at 6 and 12 months post randomization, in both groups. At the time of

randomization, all patients underwent echocardiography at a similar eGFR and prior to commencing dialysis; for patients in whom dialysis had been initiated (6 and 12 month echocardiograms), this occurred on the day following dialysis for hemodialysis patients. The 12 month echo was performed 12 months post randomization. The six month interim echocardiogram was intended to assess the timing of any changes should they be observed. During the study it became apparent that the six month data was likely to be incomplete (less than 50%), mostly due the need for an additional visit at a time when many were commencing dialysis. Therefore, a decision was made to only analyze and report the baseline and 12 month echocardiographic data.

Echocardiographic Endpoints

The primary endpoint of our study was LVMi, a measure of cardiac hypertrophy. Before the study commenced, we determined secondary echocardiographic endpoints on the basis of structure and function a) cardiac structure (LVH): LVMi (M-mode or 2D), LVMi to volume ratio; myocardial fibrosis; b) left ventricular systolic function (in order of priority): LV ejection fraction (LVEF), tissue Doppler annular systolic velocity (Sa), LV end-systolic volume index, preload corrected stroke work; c) Left ventricular diastolic function (in order of priority): left atrial volume, mitral Doppler filling pattern, pulmonary venous Doppler atrial reversal duration – mitral A wave duration (PVARD-MAD); d) Left ventricular filling pressure E:Ea. These endpoints were carefully selected due to prior reported associations with CVD mortality. During the study, changes were made to the sub-study study endpoints: firstly, it became apparent that there would be insufficient data to reliably measure myocardial backscatter or pulmonary venous Doppler and these end points were dropped. Secondly, we elevated a single endpoint from each category (LVEF, LAVi, E:Ea) to primary endpoint status alongside LVMi.

Derivation of endpoints

LVMi was primarily determined by the area-length 2D method using apical 4-chamber and parasternal short axis images at end-diastole[13]. Where 2D images were inadequate quality, m-mode measurements were substituted. LVEF was derived from LV volumes assessed by the biplane modified Simpson's method (from apical four and two-chamber views). Left ventricular mass (LVM) to LV volume ratio was calculated as unindexed LVM divided by LV end-diastolic volume. LA volume was measured using a single plane area-length method in the apical four-chamber view. LVM and LA volume were indexed to height (LVMi and LAVi) to account for individual variation in body size[13]; BSA and fat free mass, were not chosen as both of these might be unduly influenced by fluctuating weight in a patient with CKD. The mitral filling pattern was obtained using pulsed wave Doppler (5 mm sample volume) between the mitral leaflet tips. Mitral filling pressure was calculated as mitral E/annular E (E/Ea). Ea and Sa were measured by tissue Doppler (5 mm sample volume) at the medial aspect of the mitral valve annulus.

Echocardiography Endpoint Analysis

The echocardiographic sub-study involved two core laboratories: image analysis was performed at both and was allocated on the basis of echocardiographic endpoint. For example, structural endpoints (LVMi, LAVi, and LV volumes and LVEF) were measured by a single observer at the University of Auckland; and Doppler recordings (conventional and tissue Doppler) were assessed by a single but different observer at The University of Queensland. Both observers were blind to clinical data and randomization group allocation throughout all analyses. In all cases, multiple measurements (at least three) for each variable were taken and the mean measurement reported.

Statistical Methods

Data was stored in an excel database and subsequently merged with the main IDEAL Study database and all analyses performed independently by the CTRU (University of Auckland). The main analysis for comparison was the change from baseline to 12 months for the primary and

secondary endpoints, this was achieved using linear regression, adjusted for group and baseline value. Multivariate linear regression was used to evaluate the change in the four primary endpoints (LVMi, LA volume index, E:Ea, LV ejection fraction) in a model that included randomisation group (early or late), baseline value of the endpoint and eGFR (Cockcroft-Gault equation). To test for differences between intervention groups at baseline, Students t-test was used for all continuous variables (except for the time durations where the Mann-Whitney test was used), and Chi-squared test was used for all categorical variables. Analysis by group was based on randomized group regardless of whether the patient actually commenced dialysis or not.

Sample Size Calculation

Prior to commencing the sub-study, we performed sample size calculations for the primary endpoint (LVMi). Using recent data from the University of Auckland Core laboratory (mean LVMi=140g/m, SD 60) in a similar group of patients with CKD) the estimated sample size was: 200 patients per group to detect a 12% (16.8 g/m) change in LVMi (with 80% power, 5% significance) , allowing for 10% mortality at one year and 5-10% rate of transplantation. Similarly, 100 patients per group would detect a 17.1% difference; 90 patients per group would detect an 18.1% difference; and 80 patients per group would detect a 19.1% difference.

RESULTS

Patient Characteristics

A total of 182 patients (21.9% of all randomized IDEAL patients) consented to participate in the sub-study between July 2000 and November 2008 and were followed until November 2009. These patients were not different from those patients enrolled in the main IDEAL trial but not the echocardiography sub-study (table 1). Patients were recruited and randomized as part of the main IDEAL study to receive either early-start (N=91) or late-start dialysis (N=91). Of those, 74 (81%) and 69 (76%) (respectively) had both baseline and 12 months echocardiography images available

for primary endpoint analysis. Two patients in early-start group died before the 12 months echo was completed, compared with one death and one transplant in the late-start group (figure 1). Comparing the 41 (22.5%) patients in whom echocardiography data was not available at 12 months with those in whom it was, there were no differences at baseline in mean age (62.6±10.3 versus 60.3±12.1 years, P=0.27); mean systolic blood pressure (143.6±19.4 versus 141.9±21.0 mmHg, P=0.67); mean diastolic blood pressure (77.6±10.9 versus 77.5±10.7 mmHg, P=0.99); or presence of cardiovascular disease (46.3% versus 54%, P=0.36). But there was a trend towards a difference in peripheral vascular disease (26.8% versus 14.2%), P=0.06, and a difference in the presence of diabetes (58.5 versus 35.5%, P<0.01), which may have impacted on image quality or ability to attend for echocardiography.

The two randomized groups were well matched with respect to clinical characteristics at baseline (Table 2): there were no statistically significant differences between the groups for: mean age (61.6 versus 59.9 years); gender distribution (28 versus 37% female), body mass index (29.4 kg/m^2 in both groups), systolic (143.8 versus 140.8 mmHg) or diastolic (78.0 versus 77.1 mmHg) blood pressure, nor any biochemical measurements. A history of diabetes mellitus was common (40 versus 42%) as was dyslipidemia (66 versus 60%) in the early- and late-start groups respectively. Cardiovascular disease was present in 40% of the patients in both groups, mostly due to ischemic heart disease (29.1%) and vascular disease (17.0) with only a minority having a previous diagnosis of heart failure (3.9%) or stroke (3.9%). The group mean systolic blood pressure was 142.3±20.7 mmHg, mean diastolic blood pressure was 77.5±10.7 mmHg and BMI was 29.4±5.9 kg/m^2 (Table 2).

Initiation of Dialysis

Six patients (3.2%) didn't commence dialysis within the 12 months; of the 176 who did, 75 (41.2%) started on peritoneal dialysis (PD) and 101(55.5%) commenced hemodialysis (HD). Within the

early-start group, 3 (3.3%) never commenced dialysis, of the 88 that did commence dialysis, 43(48.8%) started on PD and 45(51.1%) commenced HD; and within the late-start group 3 (3.3%) never commenced dialysis, of the 88 that did commence dialysis, 32(36.3%) started on PD and 56(63.6%) commenced HD. The median time from randomization to initiation of dialysis was 1.57 months (95% CI:1.33-2.37) in the early-start group as compared with 8.63 months (95% CI:5.77-11.43) in the late-start group At the time of initiation of dialysis the mean estimated GFR as calculated from the Cockcroft-Gault equation was 12.24 mls/min/1.73m^2 (SD 3.18) in the early-start group compared with 9.66 mls/min/1.73m^2 (SD 2.89) in the late-start group, and using the MDRD equation: 9.09 mls/min/1.73m^2 in the early-start group and 6.91 mls/min/1.73m^2 in the late-start group.

Echocardiography Endpoints

At baseline, the mean value for all measures of cardiac structure was at or beyond the upper limit of normal reference ranges, including LV end-diastolic dimension (55.2±7.2 mm), LV posterior wall thickness (11.9±2.1 mm), septal thickness (11.6±2.1 mm), LV end-diastolic volume (104.5±37.8 ml), LA volume (96.1±37.7 ml), suggesting that a large proportion of values were elevated in this group (table 3). Similarly, mean diastolic measures indicate significant diastolic dysfunction within the group: Mitral E:A was lower than normal (1.00±0.49), mitral deceleration time prolonged (241.9±63.3 ms), and E:Ea was elevated (14.0±5.5). Conversely, two measures of systolic function were not as significantly abnormal: mean LV ejection fraction (LVEF) was 60.2±9.9 % and mean Sa was 6.41±1.63 m/s) and 17 (9%) patients had systolic dysfunction, defined as an LVEF of less than 50%. Of the primary echocardiographic endpoints, no differences were detected either between the groups at 12 months: overall change LVM index = 5.32 g (SE 5.27) P=0.32; LA volume index = 2.12 (SE 3.21) P=0.51; E:Ea = 0.91 (SE 0.907) P=0.31); or LVEF = 0.013 (SE 1.64) P=0.99(figure 2). No differences were detected in any other echocardiographic variable from baseline to 12 months (table 3). Similarly, no differences were observed when the analysis was performed on the

basis of dialysis type (supplementary tables 1 and 2), although there was a difference in E:Ea at 12 months (higher in the late start peritoneal dialysis group (supplementary table 2). The only parameters that reached significance in the multivariate models investigating change in the four primary endpoints (LVMi, LA volume index, E:Ea, LVEF) was the baseline measurement of the variable (all P<0.01) and no overall model was significant (table 4). When these analyses were restricted to the 63.7% (N=100) of patients with LVH at baseline (based on ASE criteria[13]) the same pattern was observed (supplementary table 3). When this was restricted to those patients in whom at least six months of dialysis was complete (n=104) we observed similar findings: that randomization to the early or late groups did not predict the change from baseline to 12 months for any of the primary endpoints, but the baseline value of eGFR was predictive of E:Ea in those with >6 months of dialsysi (supplementary table 4).

DISCUSSION

Cardiovascular disease is a major cause of death in patients with CKD[1] and heart failure is one of the major contributors to this disease burden. The IDEAL trial[12] showed that early initiation of dialysis (hemodialysis or peritoneal dialysis) in patients with advanced CKD had no significant effect on all-cause mortality or cardiovascular events. The current study extends these findings by demonstrating that planned early initiation of dialysis did not result in differences in any echocardiographic variables of cardiac structure and function. To our knowledge, this is the first randomized controlled trial to test the impact of dialysis upon cardiac structure and function.

The present study also found evidence of significant abnormalities in many echocardiographic variables in patients with stage V CKD at baseline. In almost all cases, the mean values for the groups were at the upper limits of normal, suggesting that the majority of patients had enlarged and hypertrophied hearts, diastolic dysfunction and elevated filling pressures. Interestingly, measures of systolic function were not as markedly abnormal. These findings are in keeping with those of

previous echocardiographic studies of CKD patients.[4,23]An important, novel finding of the current study was that all of these cardiac structural and functional parameters showed no significant or appreciable changes when re-examined 12 months later.

Echocardiography in patients with CKD frequently reveals LVH, volume overload, diastolic and systolic dysfunction; all precursors for the development of heart failure[2]. Although LVH is often a precursor of clinical heart disease and heart failure, increased left ventricular mass (LVM), the echocardiographic marker of LVH, is also an important (and modifiable) risk factor in its own right and is commonly associated with CKD.[3,4] However, LVM was not appreciably altered at 12 months in these patients.

Previously published observational and case-control studies in this area have reported conflicting observations. Some reports suggest that initiation of dialysis may lead to an increase in LVM.[14,15] This could be due to multiple factors, including arteriovenous fistula creation,[14] responses to volume depletion,[16] and retention of sodium and water.[17] Conversely, several studies have shown that renal replacement therapy may impact positively by reducing patients' LVM.[9,7] The inconsistency of these data may reflect the fact that these studies were non-randomized, rarely studied the same patients in a longitudinal manner, and were often subject to potential confounding, including referral time and lead time. None of these factors apply to the IDEAL trial presented here: the same patients were studied before initiation of dialysis and 12 months after initialization of dialysis.

Since we found no impact on any structural measures, it is perhaps not surprising that none of the functional measures (systolic nor diastolic) were impacted by dialysis either. Yet, we did find significant abnormalities in many echocardiographic variables at baseline. All of these remained abnormal at 12 months, and no changes in any were observed. Unfortunately our data do not allow

speculation about the hierarchy of abnormalities that exist nor the timing of these in relation to CKD duration.

This study has a number of limitations. Firstly, echocardiography was planned at six months following dialysis initiation to provide interim data and to evaluate the timing of any changes, but was incomplete and therefore unusable. Since no change was observed at 12 months, it is unlikely that these data would have revealed any further information. Secondly, this study was conducted over multiple sites over a long time period and there may have been fluctuations in the echocardiographic imaging technique. However, all of the images were analyzed at a core laboratory by a single observer, such that the measurement variation was minimized. When image quality was unreliable, we excluded those measurements; in some cases predefined endpoints (myocardial fibrosis and pulmonary venous Doppler) were unable to be included at all. Since no significant differences were detected in any of the other echocardiographic measurements, it is very unlikely that these would have yielded different results. Thirdly, recruitment for this study was difficult resulting in a smaller number of patients than planned, and based on final numbers, the study was powered to detect a 20% difference in LVMi. However, given that all variables remained static during the time, it is unlikely that an effect would have been detected even with a larger sample. We re-assessed the sample size based on the differences observed in each group and found that following required sample sizes would be required to detect a significant difference ($p=0.05$, 80% power): LVMi N=2248 (N= 3057 (90% power); E:Ea N=1527; and LA volume index N=2177. Lastly, there is the possibility that the use of magnetic resonance imaging, which offers superior resolution and inter-observer and test-retest reproducibility for assessment of LVMi, or advanced echocardiography, may have detected a smaller change in LVMi between the groups or small functional changes in the heart, although our data suggest that large, clinically significant changes were not observed.

In conclusion, planned early initiation of dialysis did not result in differences in any echo variables of cardiac structure and function in this group of patients with stage V CKD . Significant, and clinically relevant cardiac disease, including LVH, was present at baseline and remained unchanged after 12 months. These findings are consistent with the primary finding of the IDEAL study that planned early initiation of dialysis had neither beneficial nor deleterious cardiovascular impact upon patients with end-stage kidney disease.

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List of figures and tables

Figure 1 - Patient Flow

Figure 1

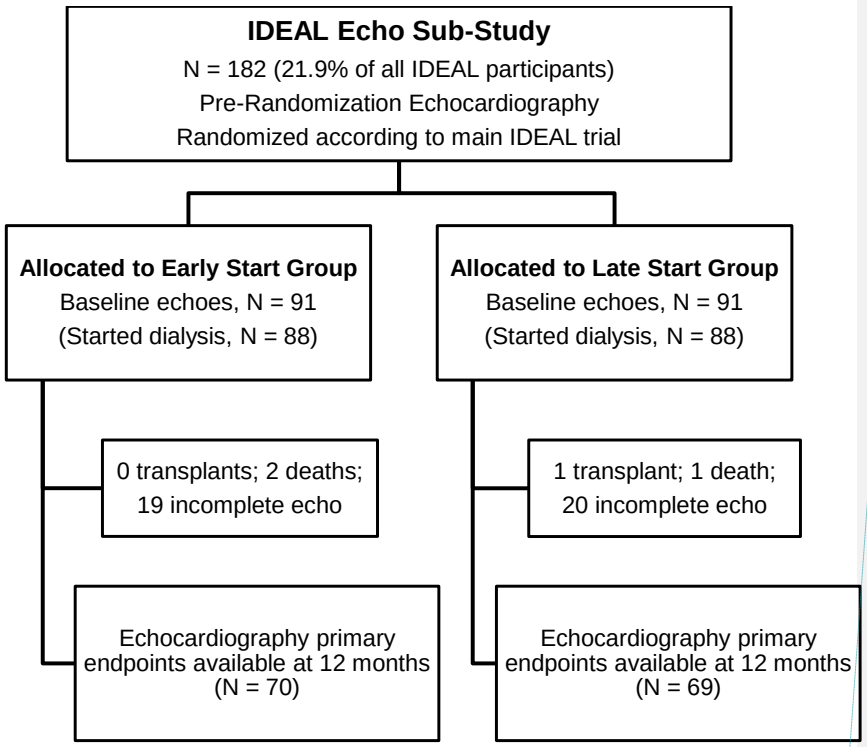

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Table 1 – Sub-study versus main IDEAL trial patients

	IDEAL TRIAL Not enrolled in Echo Sub-study N = 646	IDEAL TRIAL Echo Sub-study Patients N= 182	p value diff*
Female	227 (35.1%)	59 (32.4%)	0.5
Age, years	60.3 (12.7)	60.8 (11.7)	0.6
Months since first nephrology consultation	30.4 (10.1-74.5)	33.2 (9.7-87.7)	0.6
eGFR (C+G)	13.1 (1.4)	13.0 (1.5)	0.2
eGFR (MDRD)	9.9 (2.3)	9.7 (2.2)	0.3
BMI, kg/m^2	28.8 (6.1)	29.4 (5.9)	0.2
Systolic blood pressure, mmHg	142.6 (20.6)	142.3 (20.7)	0.9
Diastolic blood pressure, mmHg	79.2 (11.4)	77.5 (10.7)	0.08
Cardiovascular comorbidity			
Diabetes %	43.5	40.7	0.5
Hyperlipidemia %	60.2	63.2	0.5
Any cardiovascular disease %	38.5	40.1	0.7
Congestive Cardiac Failure %	5.9	3.9	0.3

Table 2 - Baseline clinical data

	Whole Group N = 182	Early-start N= 91	Late-start N=91	p value diff*
Female	59 (32.4%)	25 (27.5%)	34 (37.4%)	0.2
Age, years	60.8 (11.7)	61.6 (11.8)	59.9 (11.7)	0.3
Months since first nephrology consultation	33.2 (9.7-87.7)	40.3 (8.9-90.9)	29.2 (10-87.2)	0.8
eGFR (C+G)	13 (1.5)	13 (1.5)	13 (1.4)	0.9
eGFR (MDRD)	9.7 (2.2)	9.8 (2.2)	9.6 (2.2)	0.5
Planned dialysis mode at baseline (% hemodialysis)	46.2 %	46.2 %	46.2 %	1.0
BMI, kg/m^2	29.4 (5.9)	29.4 (5.4)	29.4 (6.3)	0.9
Systolic blood pressure, mmHg	142.3 (20.7)	143.8 (21.7)	140.8 (19.5)	0.3
Diastolic blood pressure, mmHg	77.5 (10.7)	78 (9.7)	77.1 (11.7)	0.6
Biochemical data				
Creatinine	537.9 (119.5)	536.1 (111.5)	539.7 (127.8)	0.8
Albumin	39.2 (4.5)	39.6 (4.3)	39.8 (4.7)	0.2
Calcium	2.4 (0.2)	2.3 (0.2)	2.4 (0.2)	0.3
Phosphate	1.8 (0.4)	1.8 (0.3)	1.8 (0.4)	0.7
Cholesterol	4.6 (1.4)	4.7 (1.6)	4.4 (1.1)	0.3
Triglycerides	2.5 (3.0)	2.8 (4)	2.2 (1.2)	0.2
Hemoglobin	113.8 (16.5)	115.2 (16.4)	112.3 (16.6)	0.2
Parathyroid hormone	24.7 (11.5-44.4)	25.4 (13.3-49)	23.4 (8.9-40.9)	0.8
Existing cardiovascular disease				
Diabetes %	40.7	39.6	41.8	0.8
Hyperlipidemia %	63.2	65.9	60.4	0.4
Any cardiovascular disease %	40.1	41.8	38.5	0.7
Congestive Cardiac Failure %	3.9	3.3	4.4	0.7
Peripheral Vascular Disease %	17.0	18.7	15.4	0.6
Ischemic Heart Disease %	29.1	28.6	29.7	0.9
Stroke %	3.9	5.5	2.2	0.3
Current Cardiovascular Medications				
ACE Inhibitors %	49.5	56.0	42.9	0.08
Angiotensin II Receptor Antagonist %	24.2	23.1	25.3	0.7
Statin %	61.5	68.1	54.9	0.07

* difference is between early and late start groups.
If not stated, data are mean (sd) expect for months since first nephrology consultation and parathyroid hormone, which are median (IQR)
Abbreviations: ACE = angiotensin converting enzyme; BMI = body mass index; eGFR = estimated glomerular filtration rate.

Table 3 – Echocardiographic data at baseline and 12 months

	Baseline Visit						12 Month Visit		Early vs Late Group Change from Baseline			
	N	Whole Group mean ± sd	Early-start mean ± sd	Late-start mean ± sd	Between Groups P value	N	Early-start mean ± sd	Late-start mean ± sd	mean	95%CI	P value*	N
Cardiac structure, m-mode measurements												
LV end-diastolic dimension, mm	164	55.2 ± 7.2	55.1 ± 6.0	55.3 ± 8.3	0.9	162	53.0 ± 5.9	54.4 ± 7.7	1.07	-0.95, 3.09	0.3	126
LV end-systolic dimension, mm	164	34.3 ± 7.5	34.5 ± 6.6	34.2 ± 8.4	0.8	162	31.7 ± 5.7	33.0 ± 7.8	1.03	-0.79, 2.86	0.3	126
LV posterior wall thickness, mm	164	11.9 ± 2.1	12.0 ± 2.0	11.6 ± 2.1	0.6	162	11.6 ± 2.0	11.9 ± 2.3	-0.06	-0.67, 0.55	0.9	126
LV interventricular septal thickness, mm	164	11.6 ± 2.1	11.5 ± 2.0	11.8 ± 2.2	0.7	162	11.9 ± 2.2	11.8 ± 2.1	0.31	-0.39, 1.01	0.9	126
Cardiac structure, 2D measurements												
LV end-diastolic volume, ml	147	104.5 ± 37.8	104.4 ± 29.0	104.6 ± 45.0	0.8	146	90.1 ± 26.9	100.4 ± 39.8	5.17	-4.89, 15.23	0.3	106
LV end-systolic volume, ml	147	43.3 ± 23.7	42.8 ± 18.8	43.7 ± 27.9	0.8	146	42.8 ± 18.8	39.9 ± 24.2	0.27	-5.73, 6.27	0.9	106
LA volume, ml	164	96.1 ± 37.7	96.4 ± 34.1	95.7 ± 41.6	0.9	142	88.7 ± 40.4	90.0 ± 35.2	3.54	-7.27, 14.36	0.5	98
LV systolic function measurements												
Sa, cm/s	155	6.41 ± 1.63	6.36 ± 1.69	6.45 ± 1.58	0.7	150	6.48 ± 1.45	6.45 ± 1.44	-0.08	-0.63, 0.46	0.8	98
LV diastolic function measurements												
Mitral E velocity, cm/s	157	73.2 ± 24.7	71.2 ± 25.8	75.3 ± 23.4	0.3	156	70.3 ± 20.9	72.1 ± 21.3	2.47	-4.46, 9.39	0.5	114
Mitral A velocity, cm/s	157	78.7 ± 22.0	78.3 ± 20.0	79.3 ± 23.9	0.7	156	79.5 ± 21.3	80.1 ± 20.8	1.80	-4.36, 7.96	0.6	114
Mitral E deceleration time, ms	157	241.9 ± 63.3	248.5 ± 60.0	235.4 ± 66.1	0.2	156	245.0 ± 51.7	229.1 ± 58.3	10.65	-7.64, 28.93	0.3	114
Mitral A duration, ms	157	128.3 ± 25.0	129.5 ± 21.0	127.2 ± 28.6	0.6	150	132.9 ± 19.9	130.3 ± 21.2	-1.81	-8.83, 5.21	0.6	106
Pulmonary venous A duration, ms	121	105.6 ± 22.1	109.2 ± 21.0	102.2 ± 23.0	0.08	118	107.2 ± 26.4	103.2 ± 18.9	-4.07	-13.29, 5.16	0.9	92
Ea, cm/s	160	5.69 ± 1.9	5.45 ± 1.9	5.93 ± 1.9	0.1	160	5.37 ± 1.5	5.43 ± 1.6	-0.14	-0.67, 0.39	0.6	118
Calculated variables												
LV mass index, g/m	157	135.4 ± 39.5	133.6 ± 36.7	137.2 ± 42.2	0.6	156	126.3 ± 32.2	137.7 ± 46.9	10.65	-7.64, 28.93	0.3	120
LV mass/LV volume g/ml	133	2.29 ± 0.68	2.20 ± 0.63	2.38 ± 0.72	0.1	128	2.40 ± 0.66	2.47 ± 0.84	-0.09	-0.38, 0.20	0.5	94
LA volume index, ml/m	149	56.7 ± 21.6	56.9 ± 19.9	56.5 ± 23.4	0.9	142	52.7 ± 24.0	53.3 ± 20.1	2.12	-4.25, 8.49	0.5	98
LV ejection fraction, %	147	60.2 ± 9.9	60.0 ± 9.3	60.8 ± 23.1	0.8	176	61.8 ± 10.5	61.8 ± 23.2	0.0001	-0.03, 0.03	0.9	106
E:A	157	1.00 ± 0.49	0.95 ± 0.45	1.04 ± 0.53	0.3	156	0.93 ± 0.36	0.95 ± 0.41	0.47	-0.05, 0.14	0.9	112
E:Ea	154	14.0 ± 5.5	14.0 ± 5.2	13.9 ± 5.9	0.9	152	14.1 ± 5.2	14.0 ± 5.1	-0.01	-0.03, 0.01	0.3	112

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data are mean (sd), * linear regression adjusted for baseline value and group allocation. Abbreviations: LV = left ventricle, LA= left atrium, E = early passive mitral velocity, A = active late mitral velocity; Sa = systolic mitral annular tissue Doppler velocity; Ea = early mitral annular tissue Doppler velocity; E:A = ratio of mitral early to late velocities; E:Ea = ratio of mitral early to annular velocity

Table 4 – Multivariate models for primary endpoints

Whole Group							
Endpoint	**Parameter**	**Estimate**	**SE**	**t Value**	**P Value**	**N**	**R-Square**
LV ejection fraction, %						109	0.15
	Intercept	-0.16	0.09	-1.8	0.07		
	Treatment group EARLY	0.0004	0.02	0.02	0.9		
	Baseline LVEF	0.34	0.08	4.14	<.0001		
	Baseline eGFR (C + G)	-0.004289559	0.006	-0.77	0.4		
LV mass index (g/m)						119	0.17
	Intercept	-32.16	25.18	-1.28	0.2		
	Treatment group EARLY	3.83	5.23	0.73	0.5		
	Baseline LV mass index	0.30	0.06	4.81	<.0001		
	Baseline eGFR (C + G)	-0.65	1.84	-0.36	0.7		
LA volume index (ml/m)						102	0.10
	Intercept	-19.26841702	15.14248915	-1.27	0.2		
	Treatment group EARLY	1.98692072	3.23269833	0.61	0.5		
	Baseline LA volume index	0.248361205	0.07795094	3.19	<0.01		
	Baseline eGFR (C + G)	0.609791307	1.08477884	0.56	0.6		
E:Ea						117	0.26
	Intercept	-0.147796577	0.04267033	-3.46	<0.001		
	Treatment group EARLY	20.56894268	64.60987699	0.32	0.8		
	Baseline E:Ea	0.657924828	0.06692047	9.83	<.0001		
	Baseline eGFR (C + G)	-17.72544042	21.89290587	-0.81	0.4		