Prognostic value of left atrial size in chronic kidney disease

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Aims Patients with chronic kidney disease (CKD) have high cardiovascular risk. Although stress imaging provides accurate risk estimation in this population, it is unknown if combinatorial cardiac imaging adds incremental value.

Methods and results We performed transthoracic echocardiography and stress single photon emission computed tomography (SPECT) to assess their value in predicting late cardiovascular disease (CVD) mortality in 200 patients with creatinine clearance, 60 mL/min without a history of coronary heart disease. During a median follow-up duration of 3.7 (3.5–4.0) years, there were 25 deaths because of CVD. Older age, abnormal SPECT, and increased indexed left atrial (LA) diameter were associated with CVD mortality on univariate analysis with \( P = 0.007 \), 0.01, and 0.004, respectively. In multivariable analysis, indexed LA diameter \( > 24 \) mm/m\(^2\) was independently predictive of CVD mortality [hazard ratio (HR) 2.75, confidence interval (CI) 1.14–6.59], but abnormal SPECT was not. Each mm/m\(^2\) increase in indexed atrial diameter was associated with an HR 1.20 (95% CI 1.06–1.37).

Conclusions In patients with CKD, the indexed LA diameter predicts CVD mortality independent of an abnormal SPECT result. Consideration should be given to this simple measurement as a prognostic tool in this population.

KEYWORDS
Kidney failure; Chronic; Heart atria; Echocardiography; Tomography; Emission-computed

Background
Chronic kidney disease (CKD) has been shown to be an important independent risk factor for cardiovascular disease (CVD), and CVD is the commonest cause of death in these patients.\(^1\) It is thus necessary to have safe non-invasive methods of risk stratification as coronary angiography carries a significant risk of worsening renal function and embolic complications.\(^2\) Although stress single photon emission computed tomography (SPECT) imaging has been shown to correlate well with angiographic disease\(^3\) and is useful in predicting death by CVD, it is unknown if simple echocardiographic parameters can add prognostic value to clinical variables and stress imaging in these high-risk patients. We therefore aimed to assess the incremental prognostic utility of rest echocardiographic variables, in particular the left atrial (LA) diameter, in predicting CVD mortality in patients with CKD.

Methods
Study subjects
This was an observational cohort study conducted at a single tertiary center specializing in the care of cardiac and renal diseases. The study cohort comprised 200 patients with CKD who underwent concurrent transthoracic echocardiography and stress SPECT between 1st January 1998 and 31st December 2000. CKD was defined as glomerular filtration rate \(< 60 \text{ mL/min} \cdot 1.73 \text{ m}^2\) as estimated by the Cockroft–Gault equation using two serum creatinine samples drawn at least 3 months apart.\(^1\) We excluded patients with atrial fibrillation, a history of myocardial infarction, pathological Q waves on the electrocardiogram, known serious congenital or valvular heart disease, and/or malignancy. This study was approved by the National Healthcare Group Domain Specific Review Board, and all patients gave written informed consent.

Outcomes ascertainment
We selected CVD mortality (death because of myocardial infarction, heart failure, or stroke) as the prespecified endpoint for the following reasons:

(1) National death records provided comprehensive cause of death data.
(2) Death was a suitable outcome despite the small sample size, as this was a high-risk cohort with long follow-up periods of up to 5 years.

(3) LA size has a pathophysiological link to cardiovascular endpoints.4

Imaging techniques

All echocardiographic studies were performed by experienced sonographers using a Sonos 5500 (Hewlett Packard, Andover, MA) phased-array system or Accuson Sequoia C256 (Siemens, Mountain View, CA) and reviewed by staff cardiologists with advanced training in echocardiography.

The LA diameter was assessed by M-mode echocardiography from the parasternal short-axis view using the LA anteroposterior diameter. LA diameter was then indexed to the body surface area. The patients were divided into two groups using the median-indexed LA diameter as the cut-off (Table 1)5.

All patients further underwent SPECT imaging using a standard stress-rest protocol. Technetium 99 m tetrofosmin was injected at pre-specified timings and a stress SPECT scan was then performed with a Millenium VG 5/8’ gamma camera (GE Healthcare, UK). This was followed by a rest scan 4 h later. Images were analysed with the Genie software (Genie version 2.6S, GE Healthcare, UK) regardless of whether defects were reversible (partial or total normalization on redistribution imaging) or fixed. Vanzetto and colleagues have previously demonstrated the usefulness of this method for predicting cardiovascular mortality in a large cohort of patients.5

Statistical methods

Continuous data were expressed as median (25th and 75th percentiles) unless otherwise specified. The Wilcoxon rank sum test was used for comparisons of continuous variables and the $\chi^2$ test was used for categorical variables.

CVD mortality was plotted according to the Kaplan–Meier method, and death rates were compared by the log-rank test. We further performed Cox regression analysis of survival time to cardiovascular death adjusting for variables deemed clinically important: age, gender, race, DM, creatinine clearance, use of renal replacement therapy, LA diameter index, visual ejection fraction, left ventricular inflow pattern, deceleration time, wall motion score index, left ventricular mass, presence of mitral annular calcification on echocardiography, and the presence of perfusion defect on stress SPECT. The incremental prognostic value of LA diameter

![Table 1 Baseline characteristics](https://academic.oup.com/ehjcimaging/article-abstract/9/6/736/2402831/10.1111/j.1751-752x.2008.00414.x?redirected=true)
was assessed in four modelling steps beginning with a composite $\chi^2$ value for clinical variables, and sequentially adding stress SPECT, echocardiographic variables (without LA diameter index) and lastly LA diameter index to determine the increase in $\chi^2$ value with each modelling step. Additionally, receiver-operating characteristic curves were assessed to determine the optimized LA diameter index cut-point predicting CVD mortality. All analyses were performed using SPSS version 11.5 (SPSS Inc, Chicago, IL).

**Results**

We studied 200 patients with a median age of 62.6 years (range 18–87). There were 110 (55%) male patients, and the median estimated glomerular filtration rate was 12 mL min$^{-1}$ per 1.73 m$^2$ (range 4–47). The number of patients requiring haemodialysis and peritoneal dialysis was 85 (42.5%) and 32 (16%), respectively. Ten patients were renal transplants recipients. The median indexed LA diameter was (21–27.5) 24.0 mm/m$^2$, and the median indexed LA diameter was $>24$ mm/m$^2$ in 97 patients (49%). The two groups had fairly similar baseline clinical characteristics except for more women in the group with indexed LA diameter $>24$ mm/m$^2$ (Table 1). Patients with indexed LA diameter $>24$ mm/m$^2$ had larger left ventricular dimensions as well as a greater prevalence of mitral annular calcification and moderate or severe mitral regurgitation.

During a median follow-up duration of 3.73 (3.46–4.01) years, 66 patients (33% of the study population) died. Twenty-five deaths (38% of all deaths) were attributed to CVD. Older age, an abnormal stress SPECT result, and increased indexed LA diameter were associated with CVD mortality on univariate analysis with $P = 0.004$, respectively, while reduced visual ejection fraction ($P = 0.002$ for change in $\chi^2$ value) for clinical variables, and sequentially adding stress SPECT, and echocardiographic variables from 18.9 to 21.7 with $P = 0.002$ for change in $\chi^2$.

In the receiver operating characteristic analysis, a higher LA diameter index was seen to provide greater specificity but poorer sensitivity in predicting CVD, with a c-statistic of 0.76 (Figure 4). A LA diameter index of 26.2 mm/m$^2$ offered the optimal balance between sensitivity (56%) and specificity (74%).
Discussion

Our study showed that LA diameter has independent prognostic value and provides a small but significant increment to clinical variables and SPECT imaging for predicting CVD mortality in patients with advanced CKD but preserved left ventricular systolic function. The prognostic value of the LA diameter in our study is consistent with other studies investigating its predictive value in elderly community-based populations. Moreover, our study expands these data by demonstrating the independent predictive value of the LA diameter above that provided by a comprehensive list of clinical covariates and SPECT imaging.

Age was the only other independent clinical predictor of long-term CVD mortality. A similar study by Patel and colleagues on patients with CKD awaiting renal transplantation also showed that clinical variables were not independently predictive of cardiac events when SPECT results were taken into account. This may be a situation that is unique to the CKD population where the overall prevalence of clinical risk factors is already very high. Our cohort would be considered particularly high-risk, given that most patients had very low glomerular filtration rates.

Abnormalities of diastolic filling on Doppler echocardiography were present in 38.5% of the study population but were not predictive of CVD mortality. Two reasons may account for the unexpected low prevalence of diastolic dysfunction in our study: first, a substantial number of patients were on dialysis, and all echocardiograms were obtained post-dialysis for optimal patient comfort. Therefore, filling pressures may not have been substantially elevated at the time of echocardiography, accounting for the lower proportion with grade 2 and 3 diastolic dysfunction. Second, the median age of our study population was 63 years, and the stricter age-specific criteria of diastolic dysfunction applied to this age group might have resulted in relatively low prevalence of diastolic dysfunction. Recent work has shown that Doppler indices of diastolic filling are very load dependent, fluctuating widely with changes in intravascular status during dialysis. This is especially evident in patients undergoing haemodialysis. In our study, 42.5% of patients were on haemodialysis, possibly explaining why abnormalities of diastolic filling were not predictive. On the other hand, LA size which was previously shown to correlate with LV diastolic dysfunction may be a more stable measurement that is preload independent. A recent study by Barberato and colleagues showed that fluctuations in LA size were less pronounced than changes in doppler indices of diastolic filling during haemodialysis. In our study, indexed LA diameter > 24 mm/m² had incremental predictive value beyond clinical and SPECT variables. A possible explanation for its additional prognostic ability is that LA size provides a composite measure of the total haemodynamic burden of LV systolic dysfunction, diastolic dysfunction as well as significant mitral regurgitation.

Another important finding is that an abnormal SPECT showed uniform predictive value over time with early separation of the Kaplan-Meier curves (Figure 2), while the curves for LA diameter only showed clear divergence after approximately a year (Figure 1). This observation indicates that LA diameter is useful for predicting late outcomes, but not early survival in this cohort. This is possibly because LA enlargement occurs relatively slowly, reflecting
the chronic nature of the underlying haemodynamic processes that give rise to LA remodelling.

The main limitation of our study was the heterogeneous study population, including a subset of very high-risk patients requiring renal replacement therapy. It is however, noteworthy that the majority of patients in our cohort had advanced CKD (defined as GFR < 30 ml·min⁻¹ per 1.73 m²) but preserved left ventricular systolic function (defined as left ventricular ejection fraction >50%). The study findings are thus most applicable to patients with similar characteristics. Another limitation is that the LA diameter instead of LA volume was used in our relatively community-based study correlating the LA diameter with clinical outcomes. Many investigators now feel that LA volume is a more accurate measure of the LA size than LA diameter. Despite these limitations, our study shows that a simple measure such as LA diameter has incremental predictive value for CVD mortality.

In conclusion, the LA diameter index has independent prognostic value and provides a small but significant increment to clinical variables and SPECT imaging for predicting CVD mortality in patients with advanced CKD but preserved left ventricular systolic function. The LA diameter index should thus be considered an adjunct to stress testing in assessing cardiovascular outcomes for this high-risk cohort.

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References


