Reappraisal in two European cohorts of the prognostic power of left ventricular mass index in chronic kidney failure

Giovanni Tripepi[1], Bruno Pannier[2], Graziella D'Arrigo[1], Francesca Mallamaci[1], Carmine Zoccali[1] and Gerard London[3]

[1]Institute of Clinical Physiology (IFC-CNR), Research Unit of Reggio Calabria, Italy; [2]Centre Hospitalier F.H. Manhes, Fleury Merogis, France; and [3]INSERM U970, Hopital Européen Georges Pompidou, Paris, France

Left ventricular hypertrophy is a strong causal risk factor of cardiovascular morbidity and death in end stage kidney failure, and its prognostic value is taken for granted in this population. However, the issue has never been formally tested by state-of-art prognostic analyses. Therefore, we determined the prognostic power of the left ventricular mass index (LVMI) for all-cause and cardiovascular death beyond and above that provided by well validated clinical risk scores, the annualized rate of occurrence cohort risk scores (ARO, all cause death risk and cardiovascular risk). Two large cohorts that measured LVMI in 207 hemodialysis patients in the South Italian CREED cohort and 287 patients in the French Hospital Manhes cohort were analyzed. Over a two year follow-up, 123 patients died (cardiovascular death 65%). In Cox models both the LVMI and the ARO risk scores were significantly related to all-cause and cardiovascular death. In prognostic analyses, LVMI per se showed an inferior discriminatory power (Harrell's C index) to that of the ARO risk scores (all-cause death: –10%; cardiovascular death: –5%). LVMI largely failed to improve model calibration based on the ARO risk scores, and added nonsignificant discriminatory power (Integrated Discrimination Index +2% and +3%) and quite limited reclassification ability (Net Reclassification Index +4.3%, and +8.8) to the ARO risk scores. Thus, while left ventricular hypertrophy remains a fundamental treatment target in end stage kidney failure, the measurement of LVMI solely for risk stratification is unwarranted in this condition.

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Correspondence: *Prof. Carmine Zoccali, Nephrology, Dialysis and Transplantation Unit and CNR-IFC/IBIM Research Unit of Reggio Calabria, c/o EUROLINE di Barillà Francesca, Via Vallone Petrara 55-57, 89124 Reggio Calabria, Italy. E-mail: carmine.zoccali@tin.it*

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Left ventricular hypertrophy (LVH) is a hallmark of end-stage kidney failure (ESKF).[1] As much as 60% to 80% of ESKF patients[2–4] display LVH by echocardiography, and this alteration is considered to result from the integrated, long-term effects of several traditional and nontraditional risk factors directly or indirectly impinging upon the left ventricle.[1] Although factors implicated in the etiology of LVH have been intensively investigated both in observational and in experimental studies in animal models and in ESKD patients,[1] to date, no study has specifically looked at the prognostic power of this biomarker by applying state-of-art prognostic analyses, including calibration analysis,[5] discrimination analysis (Harrell's C statistics),[6] the explained variation (R^2) in relevant clinical outcomes (an index that combines calibration and discrimination),[7] and risk re-classification.[8] Regardless of symptoms, ESKD-specific cardiovascular (CV) guidelines by Kidney Disease Outcomes Quality Initiative formally recommend to perform echocardiography at initiation of dialysis and every 3 years thereafter.[9] Although this recommendation is justifiable for prevention of *de novo* or recurrent heart failure, this may not be extended to prognosis and risk stratification because the issue of whether the left ventricular mass index (LVMI) has meaningful prognostic power above and beyond simple risk prediction scores based on easily available clinical data is unknown. This is an important question, because to be used in clinical practice for prognosis, a biomarker like LVH should give prognostic information beyond and above that provided by simple and well-validated risk prediction rules.[10]

Recently, 2 simple risk prediction instruments based on easily available clinical information in ESKF patients to predict all-cause[11] and CV mortality[12] have been developed by the Annualized Rate of Occurrence (ARO) cohort investigators. Both instruments have been robustly validated in an external, large cohort, such as the third Dialysis Outcomes and Practice Patterns Study (DOPPS) cohort, a cohort that included dialysis patients in >20 countries on 4 continents.

With this background in mind, in the present study, we assessed whether LVMI adds prognostic information to the prediction power of the 2 ARO cohort instruments for predicting 2-year all-cause and CV mortality in ESKD. Our analysis was based on 2 cohorts, the Cardiovascular Risk Extended Evaluation in Dialysis (CREED) cohort in the south

of Italy and the Manes Hospital (MH) cohort in Paris. These cohorts are among the largest providing detailed clinical information and echocardiographic studies on dialysis patients.

RESULTS

The study population included 494 hemodialysis patients (Table 1). The mean age of patients was 56 ± 16 years, and 12% were diabetics. Most patients were men (59%), and approximately one-half were on antihypertensive treatment (48%) and smokers (42%). Approximately one-third of patients had background CV comorbidities (35%). Eleven percent had myocardial infarction, 8% had stroke, 11% had transient ischemic attacks, 30% had electrocardiographically documented angina episodes, and 13% peripheral vascular diseases. The remaining clinical, hemodynamic, and biochemical data of the whole study population are detailed in Table 1. Patients in the French cohort were 6 years younger, more frequently men, smokers, and on antihypertensive treatment, and they displayed higher blood pressure and LVMI compared with patients of the Italian cohort (Table 1). The prevalence of background CV comorbidities in patients in the French cohort was substantially less (24%) than that in patients of the Italian cohort (48%). Body mass index, diabetes, dialysis vintage, cholesterol, hemoglobin, albumin, phosphate, and KT/V were quite similar among the2 cohorts (Table 1).

Left ventricular hypertrophy and risk scores distribution

In the combined cohorts, LVMI (Figure 1, upper panel) was on average 59 ± 18 g/m$^{2.7}$, and the prevalence rate of LVH was 70%. The risk scores for the prediction of all-cause (Figure 2a) and CV (Figure 2b) mortality had an approximate normal distribution, and this was also true in a separate analysis of LVMI and risk scores by the cohorts (Figures 1 and 2). On univariate analysis, LVMI was significantly related to cause-specific risk scores (Figure 3) in both the whole study cohort as well as in the 2 cohorts (CREED and HM cohorts) considered separately (Figure 3). The strength of the linear association between LVMI and the 2 risk scores was almost identical in the CREED and HM cohorts (Figure 3).

Cox regression analyses

During the 2-year follow-up period, 123 patients died, 80 of them (65%) due to CV causes. Seventy-three patients (15%) were lost to the follow-up and censored at the date of the last observation. In unadjusted analysis stratified by cohort (CREED and HM cohort), LVMI was significantly related to all-cause mortality, and a 1 g/m$^{2.7}$ increase in LVMI entailed a 3% increase in the incidence rate of all-cause death (hazard ratio [HR] [1 g/m$^{2.7}$]: 1.03; 95% confidence interval [CI]: 1.02–1.04; $P < 0.001$) (Table 2). Similarly, the ARO cohort risk score significantly predicted all-cause death, and a 1-U increase in this score was associated with a 21% increase in the incidence rate of mortality (HR [1 U): 1.21; 95% CI: 1.16–1.26; $P < 0.001$) (Table 2). In multivariate analysis including the ARO risk score and LVMI, both LVMI (HR: 1.02; 95% CI: 1.01–1.03; $P < 0.001$) and the risk score (HR: 1.19; 95% CI: 1.13–1.24; $P < 0.001$) were significantly and independently associated with all-cause mortality. By the same token, LVMI and the risk score predicted CV mortality both on univariate

Table 1 | Main clinical, biochemical and echocardiographic data of the whole study population and separately in the CREED and MH cohorts

	Combined cohort (n = 494)	CREED cohort (n = 207)	MH cohort (n = 287)
Age (yr)	56 ± 16	59 ± 15	53 ± 16
Male sex (%)	59%	56%	61%
BMI (kg/m^2)	23.9 ± 4.0	24.6 ± 4.4	23.2 ± 4.0
Smokers* (%)	42%	38%	43%
Diabetics† (%)	12%	14%	10%
On antihypertensive treatment (%)	48%	38%	55%
Dialysis vintage (mos)	44 (16–92)	43 (19–105)	45 (14–84)
CV comorbidities‡ (%)	35%	48%	24%
Systolic pressure (mm Hg)	147 ± 25	140 ± 25	152 ± 25
Diastolic pressure (mm Hg)	80 ± 14	76 ± 13	82 ± 14
Heart rate (beats/min)	74 ± 11	78 ± 13	71 ± 11
Cholesterol (mmol/L)	5.19 ± 1.27	5.23 ± 1.63	5.07 ± 1.08
Hemoglobin (g/L)	10.3 ± 1.8	10.7 ± 1.9	10.0 ± 1.6
Albumin (g/dl)	4.0 ± 0.4	4.1 ± 0.8	3.9 ± 0.3
Phosphate (mmol/L)	1.71 ± 0.38	1.51 ± 0.17	1.85 ± 0.42
Kt/V	1.28 ± 0.24	1.25 ± 0.30	1.30 ± 0.18
Echocardiography			
Interventricular septum thickness (cm)	1.14 ± 0.23	1.17 ± 0.21	1.10 ± 0.23
Posterior wall thickness (cm)	1.00 ± 0.23	1.10 ± 0.20	0.92 ± 0.22
Left ventricular end-diastolic diameter (cm)	5.32 ± 0.70	5.04 ± 0.66	5.52 ± 0.66
Left ventricular mass index (g/m$^{2.7}$)	66 ± 20	61.1 ± 18.7	68.9 ± 19.9

Data are mean ± SD, median and interquartile range, or as percent frequency, as appropriate.
*Smokers: ≥1 cigarette/day.
†Diabetes was defined according to clinical history (oral antidiabetics or insulin in predialysis, and switch to insulin in dialysis).
‡Cardiovascular (CV) morbidities were defined according to classical clinical signs and treatments (complemented by the presence of stress echocardiography, angiography, angioplasties, stentings, coronary or peripheral artery bypass, myocardial infarction electrocardiographic changes/classical enzymology.