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High estimated pulmonary artery systolic pressure predicts adverse cardiovascular outcomes in stage 2–4 chronic kidney disease

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High estimated pulmonary artery systolic pressure (ePASP) is an established risk factor for mortality and cardiovascular (CV) events in the general population. High ePASP predicts mortality in dialysis patients but such a relationship has not been tested in patients with early CKD. Here we estimated the prevalence and the risk factors of high ePASP in 468 patients with CKD stage 2–4 and determined its prognostic power for a combined end point including cardiovascular death, acute heart failure, coronary artery disease, and cerebrovascular and peripheral artery events. High ePASP (35 mm Hg and above) was present in 108 CKD patients. In a multivariate logistic regression model adjusted for age, diabetes, hemoglobin, left atrial volume (LAV/BSA), left ventricular mass (LVM/BSA), and history of CV disease, age (OR, 1.06; 95% CI, 12 1.04–1.09) and LAV/BSA (OR, 1.05; 95% CI, 1.03–1.07) were the sole significant independent predictors of high ePASP. Elevated ePASP predicted a significantly high risk for the combined cardiovascular end point both in unadjusted analyses (HR, 2.70; 95% CI, 1.68–4.32) and in analyses adjusting for age, eGFR, hemoglobin, LAV/BSA, LVM/BSA, and the presence of diabetes and CV disease (HR, 1.75; 95% CI, 1.05–2.91). High ePASP is relatively common in patients with stage 2–4 CKD and predicts adverse CV outcomes independent of established classical and CKD-specific risk factors. Whether high ePASP is a modifiable risk factor in patients with CKD remains to be determined in randomized clinical trials.

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Patients with chronic kidney disease (CKD) are notoriously at very high risk for cardiovascular events and premature death.[1] Data extracted from extensive databases in Canada document that the death risk of subjects with a glomerular filtration rate (GFR) <60 ml/min per 1.73 m^2 is of the same order as that of patients who had suffered a myocardial infarction and about twice higher than that of diabetic patients without CKD.[2] Such a high risk derives from exposure to classical cardiovascular risk factors prior to CKD and thereafter to CKD-specific risk factors, encompassing anemia, protein wasting, inflammation, and CKD–metabolic bone disorders whose burden progressively increases as CKD evolves toward kidney failure.[3]

Left ventricular (LV) hypertrophy and LV function disorders are highly prevalent in CKD, and these alterations are considered powerful integrators of the overall burden of classical and CKD-specific risk factors on the cardiovascular system in this population.[4] However, even when considered in a context including simultaneous vascular disease, these disorders largely fail to explain in full the risk excess for cardiovascular events portended by CKD, indicating that other, hitherto overlooked, cardiovascular disorders have a role in the high risk for such events.

High pulmonary artery systolic pressure estimated by echocardiography (ePASP) is an emerging, novel cardiovascular (CV) risk factor in the general population.[5,6] This condition is exceedingly prevalent in asymptomatic dialysis patients.[7] Several risk factors such as volume overload, the presence of high-flow artero-venous fistulas, sleep apnea, and sympathetic hyperactivation have been postulated to explain the high risk for elevated ePASP in these patients, and some studies also documented that elevated ePASP predicts a high risk for all-cause and cardiovascular mortality in this population, as reviewed recently.[7]

ePASP evaluation in predialysis CKD patients has received very scanty attention. Only one study has so far analyzed ePASP in early CKD stages (stages 1–3),[8] whereas studies looking at ePASP in advanced CKD included mainly CKD stage 5 patients and just a small number of CKD stage 4

patients without providing separate data or targeted analyses.[9,10] In this study we therefore aimed to estimate the prevalence and prognostic implications of ePASP in a large cohort of stage 2–4 CKD patients gathered by combining two cohorts in a Department of Nephrology in Germany (the CARE FOR HOMe study cohort) and in a Renal Unit in Italy (the MAURO study cohort).

RESULTS

Patients' baseline characteristics

The main baseline characteristics of the study cohort are summarized in Table 1. The mean age of patients was 64 ± 12 years, and 60% ($n = 280$) of them were male. A total of 165 (35%) patients were diabetic and 59 (13%) were current smokers. One hundred and forty-one patients (30%) had a history of cardiovascular disease, such as transient ischemic attack, stroke, peripheral vascular disease, or ischemic cardiac disease. All patients had CKD stage 2–4. Mean serum creatinine was 1.66 ± 0.67 mg/dl with a mean estimated GFR of 45 ± 18 ml/min per 1.73 m^2 (Chronic Kidney Disease Epidemiology Collaboration formula) (CKD-EPI). Mean systolic and diastolic BP levels were 150 ± 25 and 85 ± 13 mm Hg, respectively. Median albuminuria was 0.04 (interquartile range, 0.007–0.21), mean left ventricular ejection fraction was 63 ± 10%, and mean left ventricular mass indexed by body surface area (LVM/BSA), left atrial volume indexed by body surface area (LAV/BSA), and left atrial diameter were 97.0 ± 30.7 g/m^2, 35.3 ± 12.7 ml/m^2, and 37.5 ± 12.5 mm, respectively. High ePASP values (⩾35 mm Hg) were present in 23% ($n = 108$) of patients in the study population and the prevalence of this alteration rose progressively across CKD stages (stage 2: 17%; stage 3: 24%; stage 4: 27%). In a

Table 1 | Demographic, somatometric, and clinical data of the study population

	Whole cohort ($N = 468$)	ePASP < 35 mm Hg ($N = 360$, 77%)	ePASP ⩾35 mm Hg ($N = 108$, 23%)	P
Age (years)	64 ± 12	62 ± 13	71 ± 9	**<0.001**
Male, *n* (%)	280 (60)	212 (59)	68 (63)	0.50
BMI (kg/m^2)	29 ± 5	29.6 ± 5.2	29.1 ± 4.88	0.40
Systolic blood pressure (mm Hg)	149 ± 24	149 ± 24	153 ± 27	0.11
Diastolic blood pressure (mm Hg)	85 ± 13	86 ± 13	83 ± 13	0.16
Diabetes, *n* (%)	165 (35)	118 (33)	47 (43)	**0.04**
Current smokers, *n* (%)	59 (13)	51 (14)	8 (7)	0.06
Total cholesterol (mg/dl)	190 ± 42	191 ± 42	184 ± 42	0.13
Hemoglobin (g/dl)	13.4 ± 1.6	13.5 ± 1.6	12.9 ± 1.6	**<0.001**
Albumin (g/dl)	4.4 ± 0.4	4.4 ± 0.4	4.7 ± 0.4	0.87
Serum phosphate (mg/dl)	3.4 ± 0.7	3.4 ± 0.7	3.5 ± 0.8	0.17
eGFR (ml/min/1.73 m^2)	45.2 ± 17.6	46.3 ± 17.7	41.5 ± 16.9	**0.01**
Albuminuria (g/g creatinine)	0.04 (0.007–0.21)	0.04 (0.006-0.22)	0.04 (0.009-0.21)	0.94
ePASP (mmHg)	10 (10-34)	10 (10-18)	41 (38-45)	**<0.001**
Creatinine (mg/dl)	1.66 ± 0.67	1.65 ± 0.68	1.72 ± 0.63	0.33
LVEF (%)	63 ± 10	57 ± 21	53 ± 23	0.17
LVM/BSA (g/m^2)	97.0 ± 30.7	95.2 ± 29.2	103.0 ± 34.4	**0.03**
LAV/BSA (ml/m^2)	35.3 ± 12.7	32.7 ± 11.2	43.5 ± 13.7	**<0.001**
LAD (parasternal view; mm)	37.5 ± 12.5	37.1 ± 11.7	38.7 ± 15	0.31
Fractional shortening (%)	38.0 ± 8.2	38.4 ± 7.9	36.8 ± 9.1	0.12
Anti-hypertensive drugs				
Diuretics, *n* (%)	356 (76)	260 (72)	96 (89)	**<0.001**
β-Blockers, *n* (%)	262 (56)	179 (50)	83 (77)	**<0.001**
ARBs, *n* (%)	223 (48)	161 (45)	62 (57)	**0.021**
ACEi, *n* (%)	200 (43)	160 (44)	40 (37)	**0.17**
CCBs, *n* (%)	236 (50)	184 (51)	52 (48)	**0.57**
Etiology of CKD, n *(%)*				
Cystic diseases	23 (5)	22 (6)	1 (1)	—
Diabetic nephropathy	43 (9)	31 (9)	12(11)	0.43
Glomerular diseases	66 (14)	54 (15)	12(11)	0.31
Nephroangiosclerosis	189 (40)	133 (37)	56(52)	**0.006**
Interstitial-/pyelo-nephritis	21(4)	21 (6)	0 (0)	—
Other	126 (27)	99 (27)	27(25)	0.61
History of CV comorbidities, *n* (%)	141 (30)	98 (27)	43 (40)	**0.01**
TIA, *n* (%)	20 (4)	16 (4)	4 (4)	0.74
Peripheral vasculopathy, *n* (%)	29 (6)	21 (6)	8 (7)	0.55
Coronary stent *n* (%)	59 (13)	39 (11)	20 (18)	**0.04**
Myocardial infarction, *n* (%)	52 (11)	34 (9)	18 (17)	**0.04**
Stroke, *n* (%)	31 (7)	21 (6)	10 (9)	0.21

Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; BMI, body mass index; CCBs, calcium channel blockers; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ePASP, estimated pulmonary artery systolic pressure; LAD, left atrial diameter; LAV/BSA, left atrial volume indexed by body surface area; LVEF, left ventricular ejection fraction; LVM/BSA, left ventricular mass indexed by body surface area; TIA, transient ischemic attack. Statistically significant differences between groups are in boldface.

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