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Performance of a Multi-biomarker Panel for Prediction of Cardiovascular Event in Patients with Chronic Kidney Disease

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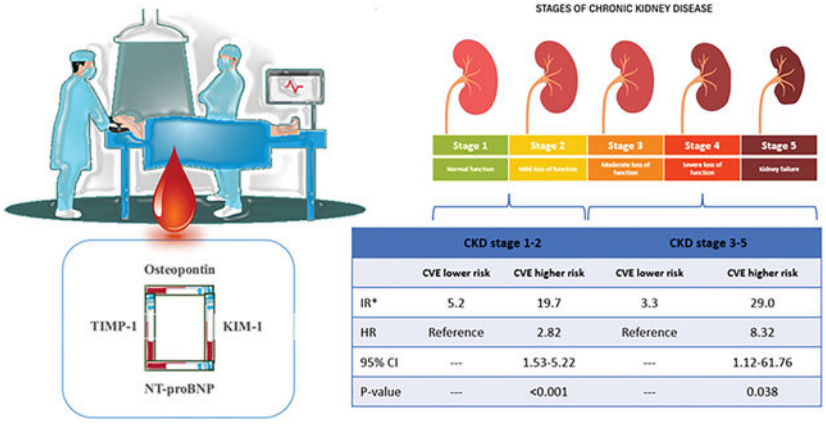
Graphical Abstract:



	CKD stage 1-2		CKD stage 3-5	
	CVE lower risk	CVE higher risk	CVE lower risk	CVE higher risk
IR*	5.2	19.7	3.3	29.0
HR	Reference	2.82	Reference	8.32
95% CI	---	1.53-5.22	---	1.12-61.76
P-value	---	<0.001	---	0.038

Introduction

Persons with chronic kidney disease (CKD) are at twofold increased risk for cardiovascular events (CVE: incident myocardial infarction [MI], stroke, or cardiovascular death) compared

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to non-CKD individuals following coronary angiography[1]. Multiple clinical factors, including diabetes mellitus, heart failure, high blood pressure, and kidney disease, have been proposed to increase the risk of CVE among CKD patients following coronary intervention[2]. Excess activation of counter-regulatory pathways such as renin-angiotensin-aldosterone and natriuretic peptide system, inflammation, endothelial dysfunction, and vascular calcification have been attributed to the elevated CV risk among patients with CKD[3]. Biomarker measurement is a parsimonious approach to gauge these underlying pathophysiologic processes. Hence, a biomarker panel may guide healthcare professionals in stratifying patients at increased risk of CVE. In this study, using a panel of biomarkers developed via targeted proteomics, we hypothesized that a distinct set of biomarkers could stratify the risk of developing CVE following coronary angiography.

Methods

To explore this question, we utilized the resources of the Catheter Sampled Blood Archive in Cardiovascular Diseases (CASABLANCA) cohort study (NCT00842868)[4]. 1251 patients were enrolled in CASABLANCA. Specific to this sub-study, we excluded those who underwent peripheral angiography (n=152), leaving 1,099 patients in this study. A subset of the 172 patients were selected as external validation. A cohort of 927 remaining patients was split with a 70:30 ratio into separate derivation and internal validation sets, resulting in a derivation set of 649 patients and an internal validation set of 278 patients. The derivation set was used to identify the prognostic panel and develop the prognostic model, and the internal validation set was initially used with the validation of this model. The validation cohort for this study consists of the combined internal and external validation sets (n = 278 + 172 = 450). Four patients had a missing estimated glomerular filtration rate (eGFR) value were removed, resulting in a final validation cohort of 446 participants (Figure 1). We applied a previously-developed biomarker panel to predict incident cardiovascular events (HART CVE, Prevencio, Kirkland WA). The detail of artificial intelligence-leveraged algorithm was described elsewhere(2). Briefly, 15 ml of blood was obtained immediately before angiography and after the completion of angiographic procedure(s) through a centrally placed vascular access sheath. The samples were processed and were stored in a −80 C freezer until analysis. After a single freezethaw cycle, 200 ml of plasma was analyzed for a panel of 109 biomarkers on a Luminex 100/200 xMAP technology platform. The 109 biomarkers were not individually chosen but were acquired in the form of a commercially available kit, known as the Myriad RBM MAP. This incorporates biomarkers that reflect a wide variety of pathways associated with plaque rupture/erosion and includes acute phase reactants, inflammatory markers, and biomarkers of atherosclerosis. Least absolute shrinkage and selection operator (Lasso)was implemented to select candidate final biomarker. Monte Carlo cross-validation with 1,000 iterations followed with 80/20 training/test split. In cases when a variable was not selected in all 1,000 Monte Carlo iterations or its coefficients had a p-value >0.05, the variable was removed, and the analysis repeated. The ultimate result of this process was our final panel of 4 proteins (N-terminal pro-B type natriuretic peptide, kidney injury molecule-1, osteopontin, and tissue inhibitor of matrix metalloproteinase-1). The prognostic model was linearly transformed into a scaled score of 0 to 10. Patients in the higher risk group had a score greater than or equal to the optimal cutoff

for the score, which was determined to be 5.526 using the optimal Youden's index (with the model's output rescaled to the range of 0 to 10). Patients in the lower-risk group had a score <5.526.

We defined CKD stage 1–2 as eGFR less than 120 mL/min/1.72m^2 and more than 60 mL/min/1.72m^2 and CKD stage 3–5 as eGFR less than 60 mL/min/1.72m^2. Patients were categorized into 4 groups: 1) CKD stage 1–2/CVE Lower-risk, 2) CKD stage 1–2/CVE Higher-risk, 3) CKD stage 3–5/CVE Lower-risk, 4) CKD stage 3–5/CVE Higher-risk, and were followed for 2 years for incident cardiovascular events. Cox proportional hazard regression was used to assess the association of four categories with incident CVE. Harrell C statistic was reported as a measure of the discrimination ability of the risk model.

Results

Of 446 patients with CKD included in this study, mean (standard deviation) age of study participants was 66.5 (11.2) years, and 29.2% (n=130) were female; 84.8% (n=378) were at stage 1–2 CKD and 15.2% (n=68) were at stage 3–5 CKD (Table 1).

During the 2-year follow-up, 74 CVE were ascertained. 51 (13.5%) events occurred in stage 1–2 CKD and 23 (33.8%) events occurred in stage 3–5 CKD. The C-statistic for predicting 2-years cardiovascular events in all 446 patients was 0.77 (0.72, 0.82). The model was well-calibrated (Hosmer-Lemeshow test p-value > 0.40). Considering patients at CVE lower-risk within each CKD staging group as a reference, the hazard ratio (95 % confidence interval) of cardiovascular events was 2.82 (1.53, 5.22) for CKD stage 1–2/CVE higher-risk, and 8.32 (1.12, 61.76) for CKD stage 3–5/CVE higher-risk (Table 2).

Discussion

The results of this study indicate the HART CVE panel identified patients at high risk of CVE among the patient population at different stages of CKD. This is important given the sharp increase in risk of CVE that occurs with a decline in GFR, particularly among patients with GFR below 60 mL/min/1.72m^2. Biomarker measurement is a parsimonious method to stratify risk for CVE in those with CKD, although a decline in kidney function may interfere with the discrimination of prognostic biomarkers. Thus, whenever possible, prognostic panels should be evaluated in the context of decline in kidney function in order to better understand how this situation affects performance. It is noteworthy that among those with CKD Stage 3–5, a "lower risk" HART CVE score was associated with similar event rates as lower-risk individuals with Stage 1–2 CKD and a more than 8-fold lower risk for events compared to study participants with corresponding kidney function and "higher risk" HART CVE score.

Four biomarkers included in the panel reflect a different aspect of underlying pathophysiologies enhanced among patients with CKD. KIM-1, a novel marker of acute kidney injury, is a transmembrane glycoprotein and highly upregulated following ischemia-reperfusion injury in the kidneys[5]. Many studies have shown adverse outcomes associated with acute kidney injury during coronary angiography[6, 7]. Osteopontin is synthesized in various tissues and has multiple roles in several biological processes, including

inflammatory response, bone resorption, vascular calcification, and extracellular matrix remodeling[8]. Increased expression of osteopontin was reported following myocardial infarction. Studies have linked elevated osteopontin level with increased cardiac fibrosis as osteopontin regulates myofibroblast differentiation and production of collage 1 production[9]. TIMP-1 is involved in the degradation of extracellular matrix. Increased expression of TIMP-1 was observed following acute pressure overload in myocardium and prolonged activation is linked to cardiac fibrosis and hypertrophy[10]. In a cohort of patients undergoing coronary angiography, TIMP-1 was an independent predictor of subsequent mortality and ischemic events[11]. Lastly, NT-proBNP is widely used in clinical practice as cardiac stress biomarker, and predictive ability of NT-proBNP for adverse outcomes among patients with coronary artery disease is well-established[12]. Given the specific role of each biomarker in the pathophysiology of cardiovascular disease, the developed panel may be used as a unique tool for prediction of CVE.

Conclusion

With the rapid rise in CKD, better tools to recognize risk and intervene proactively are needed. Biomarker panels such as HART CVE may be useful to individualize CVE risk assessment and foster aggressive primary and secondary cardiovascular prevention. Future clinical trials need to assess the efficacy of the HART CVE panel-guided approach in lowering the incidence of CVE among patients with CKD.

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Highlights

- Patients with chronic kidney disease are at increased risk of cardiovascular events following coronary catheterization. Preceding coronary catheterization is an ideal time to measure biomarkers and estimate risk for future cardiovascular events.
- Using a machine learning algorithm and targeted proteomics, we demonstrated that measuring four biomarkers (kidney injury molecule-1, N-terminal pro B-type natriuretic peptide, osteopontin, and tissue inhibitor of metalloproteinase-1) can individualize cardiovascular events risk assessment among patients with chronic kidney disease

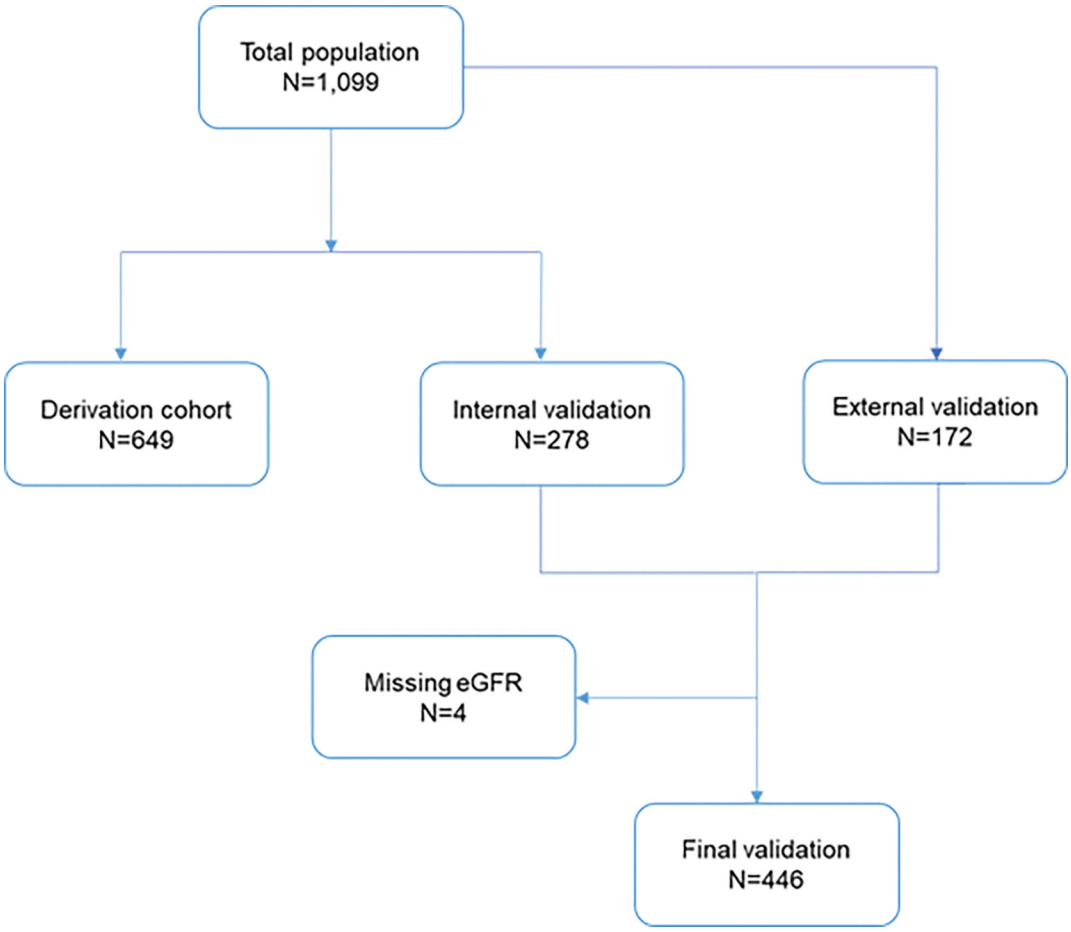

Figure 1.
CONSORT flow diagram

Table1.

Baseline characteristics of study population

variable	All	CKDs 1–2	CKDs 3–5	p-value
Age, year	66.5 (11.2)	65.6 (10.9)	71.5 (11.6)	0.001
Male	316 / 446 (70.9%)	277 / 378 (73.3%)	39 / 68 (57.4%)	0.01
Caucasian	411 / 446 (92.2%)	353 / 378 (93.4%)	58 / 68 (85.3%)	0.05
Morbidities				
Hypertension	319 / 446 (71.5%)	259 / 378 (68.5%)	60 / 68 (88.2%)	0.001
Diabetes Mellitus	113 / 446 (25.3%)	83 / 378 (22%)	30 / 68 (44.1%)	0.001
Dyslipidemia	292 / 445 (65.6%)	253 / 378 (66.9%)	39 / 67 (58.2%)	0.17
Heart failure	79 / 446 (17.7%)	56 / 378 (14.8%)	23 / 68 (33.8%)	0.001
Coronary artery disease	217 / 446 (48.7%)	173 / 378 (45.8%)	44 / 68 (64.7%)	0.005
Smoker	58 / 441 (13.2%)	52 / 373 (13.9%)	6 / 68 (8.8%)	0.33
Atrial fibrillation/flutter	83 / 446 (18.6%)	71 / 378 (18.8%)	12 / 68 (17.6%)	1
CVA/TIA	43 / 446 (9.6%)	36 / 378 (9.5%)	7 / 68 (10.3%)	0.82
Prior angioplasty	40 / 446 (9%)	33 / 378 (8.7%)	7 / 68 (10.3%)	0.65
Prior stent	120 / 446 (26.9%)	101 / 378 (26.7%)	19 / 68 (27.9%)	0.88
Prior CABG	84 / 446 (18.8%)	68 / 378 (18%)	16 / 68 (23.5%)	0.31
Laboratory tests				
Sodium, mg/dl	138.932 (3.232)	139.012 (3.117)	138.508 (3.78)	0.33
BUN, mg/dl	18 (15, 24)	17 (14, 21)	34 (26, 42.75)	0.001
Blood glucose, mg/dl	102 (91, 118)	101 (92, 116)	107 (90, 128)	0.18
Creatinine, mg/dl	1.04 (0.87, 1.28)	1 (0.84, 1.17)	1.78 (1.4, 3.78)	0.001
eGFR, ml/min/1.73 m^2	97.2 (73.9, 110.4)	102.2 (84.8, 111.8)	38.6 (18.3, 46.9)	0.001
NT proBNP, pg/mL	1550 (574, 4423)	1280 (509, 3030)	7890 (3290, 15975)	0.001
KIM-1, ng/mL	0.04 (0.02, 0.07)	0.03 (0.02, 0.06)	0.08 (0.05, 0.18)	0.001
Osteopontin, ng/mL	28 (20, 42.75)	26 (19, 37)	65.5 (37.75, 108)	0.001
TIMP-1, ng/mL	72 (58, 92.75)	68 (57, 85)	109.5 (86.5, 127)	0.001

CVA: cerebrovascular accident, TIA: transient ischemic attack, CABG: coronary artery bypass graft, BUN: blood urea nitrogen, eGFR: estimated glomerular filtration rate, NTproBNP: N terminal pro B type natriuretic peptides, KIM-1: kidney injury molecule-1, TIMP-1: tissue inhibitor of matrix metalloproteinase-1

Table 2.

Hazard ratios of cardiovascular events

Category	Incidence rate	Hazard Ratio	95% CI	P-value
Stage CKD 1–2				
CVE lower-risk	5.2	Referent	Referent	Referent
CVE higher-risk	19.7	2.82	1.53, 5.22	<0.001
Stage CKD 3–5				
CVE lower-risk	3.3	Referent	Referent	Referent
CVE higher-risk	29.0	8.32	1.12, 61.76	0.038

* Incidence rates are presented as cases per 100 person years.

Abbreviations: CKD: chronic kidney disease, CVE: cardiovascular event, CI: confidence interval