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Redefining the therapeutic strategies against cardiorenal morbidity and mortality: Patient phenotypes

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Abstract

Chronic kidney disease (CKD) patients face an unacceptably high morbidity and mortality, mainly from cardiovascular diseases. Diabetes mellitus, arterial hypertension and dyslipidemia are highly prevalent in CKD patients. Established therapeutic protocols for the treatment of diabetes mellitus, arterial hypertension, and dyslipidemia are not as effective in CKD patients as in the general population. The role of non-traditional risk factors (RF) has gained interest in the last decades. These entail the deranged clinical spectrum of secondary hyperparathyroidism involving vascular and valvular calcification, under the term “CKD-mineral and bone disorder” (CKD-MBD), uremia *per se*, inflammation and oxidative stress. Each one of these non-traditional RF have been addressed in various study designs, but the results do not exhibit any applied clinical benefit for CKD-patients. The “crusade” against cardiorenal morbidity and mortality in CKD-patients is in some instances, derailed. We propose a therapeutic paradigm advancing from isolated treatment targets, as practiced today, to precision medicine involving patient phenotypes with distinct underlying pathophysiology. In this regard we propose two steps, based on current stratification management of corona virus disease-19 and sepsis. First, select patients who are expected to have a high mortality, *i.e.*, a prognostic enrichment. Second, select patients who are likely to respond to a specific therapy, *i.e.*, a predictive enrichment.

Key Words: Cardiorenal; Morbidity; Mortality; Phenotype; Precision medicine; Personalized medicine

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Core Tip: Stagnation in the Nephrology field has to be overcome with a new perspective. This new vision takes lessons from the past as personalized medicine, adapts precision medicine from today's lessons from corona virus disease-19 and sepsis and looks into the future with the aid of the big data. Our proposal is that cardiorenal management should be stratified according to patient phenotypes and not as an assembly of individual targets.

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INTRODUCTION

Cardiovascular (CV) disease is a major contributor of mortality in chronic kidney disease (CKD) patients, especially in the late stage 5 on dialysis (5D), mounting up to 58% of causes[1,2]. Aside traditional CV risk factors (RF), as diabetes and arterial hypertension, non-traditional RF related to kidney disease *per se* seem to play a pivotal role in the complex interaction between the kidney and the heart[3]. Non-traditional RF include secondary hyperparathyroidism resulting in vascular and valvular calcification, collectively termed as CKD-mineral and bone disorder (CKD-MBD)[4], uremia *per se*, inflammation, oxidative stress and dysbiotic gut microbiota[5].

THE PROBLEM

CKD patients have long been excluded from cardiovascular clinical trials, for various reasons: (1) Inadequate surrogate outcomes and low event rate, especially in end stage renal disease, demand a prohibitory large sample size and an extensive follow up[6]; and (2) fear for negative results or adverse events, since the aforementioned non-traditional risk factors are recognized as potential disease modifiers[7]. Nephrology practice could be characterized as “low evidence” medicine, which pursues targeting traditional RF with data originating from the general, non-CKD-population[8].

Major clinical problems, such as the choice of treatment for non-valvular atrial fibrillation in dialysis patients, remain unsolved and clinical nephrologists “navigate through darkness” regarding therapeutic strategy[9]. In the case of hyperphosphatemia although there is numerous scientific evidence that “phosphate is a cardiovascular toxin”[10], there has been no randomized control trial (RCT) providing evidence that “correction” will translate into tangible cardiovascular benefit, set the optimal timing of intervention, the different means or the optimal serum phosphate target[11]. Yet the patients endure an overwhelming phosphate binder pills consumption[12] with enormous economic implications for healthcare[13].

A LIGHT IN THE TUNNEL

Sodium-glucose cotransporter-2 inhibitors (SGLT2i), initially marketed as glucose lowering drugs in diabetes mellitus type2, are a game changer in the field of cardiorenal protection[14]. Their beneficial effects, regarding reduction in CV morbidity and mortality and renal function preservation, have been assessed by RCTs across CKD stages 1-3, notably with empagliflozin (EMPA REG OUTCOME)[15] and dapagliflozin (CAPA-CKD)[16]. The unprecedented success of this novel treatment stems from the pleiotropic effects of SGLT2i, targeting multiple intra-extrarenal pathways[17].

Another promising therapeutic tool is Mediterranean Diet (Med Diet) that has a pivotal role for cardiorenal protection[18]. Targeting all traditional and multiple non-traditional RF of cardiovascular morbidity and mortality along with exercise, Med Diet confers to an anti-inflammatory and anti-oxidative metabolic profile[19]. The level of adherence has been recently linked in an observational study with left ventricular geometry patterns in dialysis patients, a powerful independent risk factor of CV mortality in this particularly vulnerable population[20].

In clinical practice SGLT2i are currently tested as real world experience in advanced stages of CKD [21]. On the other hand nephrologists are still reluctant to prescribe vegetable based diets, as Med Diet, mostly for the fear or ignorance of handling potassium and/or provoking malnutrition[22].

A KEY IN THE PUZZLE: CKD IS AN “INFLAMMAGING” CONDITION

The only positive RCT in the field of CV protection in CKD is the CANTOS trial (Canakinumab Anti-Inflammatory Thrombosis Outcome Study)[23], where the inhibition of the pro-inflammatory IL-1 β was more beneficial in post myocardial infarction patients with glomerular filtration rate (GFR) < 60 mL/min/1.73 m². The concept of “inflammaging”, introduced by Franceschi, unified all chronic degenerative conditions, in a common pathophysiology, which could be translated as a low grade sterile chronic inflammation resembling the natural course of ageing[24]. In observational studies IL-6 has been described as an independent predictor of outcome in pre-dialysis[25], hemodialysis[26] and peritoneal dialysis patients[27]. The association of inflammation and outcome seems so strong that a hypothesis proposal was made not to include inflamed and not inflamed patients in the same cohort in an RCT, since inflammation is powerful catalyst for other risk factors in CKD[28]. CKD patients are in a paradox state of both immune - paralysis (driving susceptibility to infections) and immune- activation (linked to CVD)[29].

THE SOLUTION: PRECISION AND PERSONALIZED MEDICINE

Treatment failure, targeting “traditional” RF and nontraditional RF (hyperphosphatemia, CKD- MBD parameters) stems probably from the fact that there is no stratification management that would guide a precision or personalized medicine. Nephrology practice seems to be in a state of involuntary blindness as the crowd that pretends to see the clothes of the naked Emperor in Hans Christian Andersen’s tale [30]. In order to find a solution we propose the following 4 steps: (1) Gather the wisdom of the past in the form of personalized medicine; (2) adapt precision medicine from today’s lessons from corona virus disease 19 (COVID-19); (3) sepsis; and (4) look into the future with the aid of the big data.

Personalized medicine negligence

Historically[31], the therapeutic practices have changed drastically from a “patient-centred” view to those of “evidence-based” medicine. “Germ theory of disease” in the 19th century, changed the “holistic view” perception of disease to a “specific cause for a specific disease”. The treatment approach shifted therefore, to a narrow approach that targeted a specific cause. The patient’s role diminished from an active contributor, through personal beliefs, adaptation and lifestyle choices, to a mere passive recipient of the treatment. Patients became “numbers” in any given trial, which will eventually provide the necessary information to form “therapeutic guidelines”[32]. Ironically and paradoxically, the contemporary nephrologist is called to manage CKD patients, who are at very high risk of cardiovascular morbidity and mortality, with guidelines based on weak evidence[6]. As mentioned Nephrology field lacks RCTs and the Cardiology field excludes CKD patients[7]. Furthermore, during the decision-making process the patient is a passive recipient of the diagnostic decision[32].

Precision medicine: Lessons from COVID-19

The pandemic of COVID-19 has taught us a great example of precision medicine. First it was discovered that patients respond differently to the “viral-intruder” and the host’s immune response, whether regulated or dysregulated leads to a favorable or unfavorable outcome respectively[33]. Later on, two distinct pathways were revealed[34] as well as an early biomarker for disease prediction (SUPAR-Soluble urokinase plasminogen activator receptor)[35]. This approach led to precision guided therapy with anakinra that showed remarkable benefit regarding respiratory failure and mortality[36].

Lessons from sepsis

In many aspects “sepsis” and “CKD” have many similarities. Both are heterogeneous syndromes with underlying “inflammation”. Sepsis is defined as “organ dysfunction caused by a dysregulated host response to infection”[37]. CKD is defined as kidney damage or GFR < 60 mL/min/1.73 m² for 3 mo or more, irrespective of cause[38]. Based on this definition half of people over 75 are “labelled” as CKD, but there is debate if they can be regarded as “same risk” for renal deterioration or CV morbidity and mortality as younger people with the same stage of CKD[39]. At the same time CKD has a “systemic nature”[40] affecting multiple organ pathways, on a specific epigenetic background. In parallel sepsis, despite all the achievements in understanding its pathophysiology, is now regarded as “a multifaceted disruption of the finely tuned immunological balance of inflammation and anti-inflammation”[41]. There is a trend to identify patient phenotypes in order to stratify an accurate management[42].

The promise of big data

The “big data” era of the last decade, a precious gift of the tremendous advances in computational technology has helped enormously diverse medical scientific fields, in terms of diagnosis, risk assessment and treatment, fueling precision medicine, but Nephrology field is lagging behind[43]. As an example, multi-omics data combined with clinical and demographic data helped to generate machine -

Table 1 Proposed Measures of prognostic enrichment

Category	Parameters	Evaluation method	
Laboratory	eGFR	Continuous CKD-EPI (mL/min/1.73 m ²)	Discrete based on trials CKD stages 1,2,3a/b,4,5
	uACR	Mg albumin/g creatinine	Albuminuria stages A1,A2,A3
	hs-CRP		
	Serum magnesium		
	PTH	Intact PTH (pg/mL)	KDIGO < 150, 150-500, > 500 pg/mL
Radiology	Anemia variables	Ht/Hb/TSAT/Ferritin/Hepcidin	
	LVMI	LV mass indexed to body surface area (g/m ²)	Geometry types
	Lateral abdominal X-ray	Scale from 0-24	Leena Kaupilla Score ≤ 4 vs > 4
Clinical status	Aortic stiffness	Pulse wave velocity carotid-femoral PWV (m/s)	CF-PWV < 8.8, 8.8-12, > 12 m/s
	Frailty	Nine-point clinical frailty scale	
	Aortic stiffness	Pulse pressure (mmHg)	
	Physical activity	Handgrip strength	
Co-morbidities	Diet	Mediterranean Diet Score Panagiotakos Scale 0-24	
	DM, CAD, PAD, stroke, COPD		Charlson comorbidity index
Bones	Mineral bone density (DEXA)	Values from DEXA (g/cm ²)	Ostopenia osteoporosis

eGFR: Estimated glomerular filtration rate; uACR: Urinary albumin to creatinine ratio; PTH: Parathyroid hormone; Ht: Haematocrit; Hb: Haemoglobin; TSAT: Transferrin saturation; LVMI: Left ventricular mass index; DM: Diabetes mellitus; CAD: Coronary artery disease; PAD: Peripheral artery disease; COPD: Chronic obstructive pulmonary disease; CKD-EPI: Chronic kidney disease-epidemiology collaboration formula; KDIGO: Kidney Disease: Improving Global Outcomes; CF-PWV: Carotid to femoral pulse wave velocity; DEXA: Dual energy X-ray absorptiometry.

learning models for prediction of preeclampsia[44]. Burning clinical issues regarding CKD patients, especially in advanced stages, as treatment of vascular disease, heart failure with reduced or preserved ejection fraction and prevention of sudden cardiac death do not have solid answers yet[8]. Big data science from electronic health records and longitudinal follow up could be a surrogate of RCTs assisting clinical decision[6].

PRECISION MEDICINE THROUGH PATIENT PHENOTYPES

Our hypothesis is that there could be a paradigm shift in the field of nephrology regarding patient stratification and targeted management. In order to accomplish this transition the search for «biomarkers» could be helpful, as in sepsis[45]. The first step of a “prognostic enrichment”, *i.e.*, select patients who are suspected to have high mortality, could be followed by “predictive enrichment”, *i.e.*, patients who are likely to respond to a specific therapy (Figure 1). In this regard various biomarkers could be tested alone or in combination as: (1) Those already used in clinical practice (Table 1); and (2) the established biomarkers of cardiorenal syndrome[46] and those that could be found from multi-omics technology (blood and/or urine samples)[47].

One example of prognostic enrichment in nephrology involves the “heat map” based on GFR levels and albuminuria. It has been extensively validated and has a broad clinical application[48,49]. The CORD study in hemodialysis patients showed that vascular calcification (assessed from plain lateral abdominal X-ray), and arterial stiffness (measured by carotid-femoral pulse wave velocity) are independent prognostic markers of adverse outcome[50].

Regarding predictive enrichment one could utilize CORD study as an implementation paradigm (Figure 2). The authors showed that increased arterial stiffness-associated CV risk, is less pronounced at higher levels of calcification. Also an impressive number (19% of 993 pts “non - calcifiers” *i.e.*, with no visible calcification deposits in lateral X-ray) was identified[51]. This implies the existence of genetic predisposition. This heterogeneity of the dialysis patient population could be contributing to the inconclusive results of the EVOLVE trial. In this study, lowering parathormone levels and targeting adverse CKD-MBD parameters as serum phosphorus and vascular calcification did not produce a statistically significant benefit in preventing CV events[52]. Another example is the interaction between

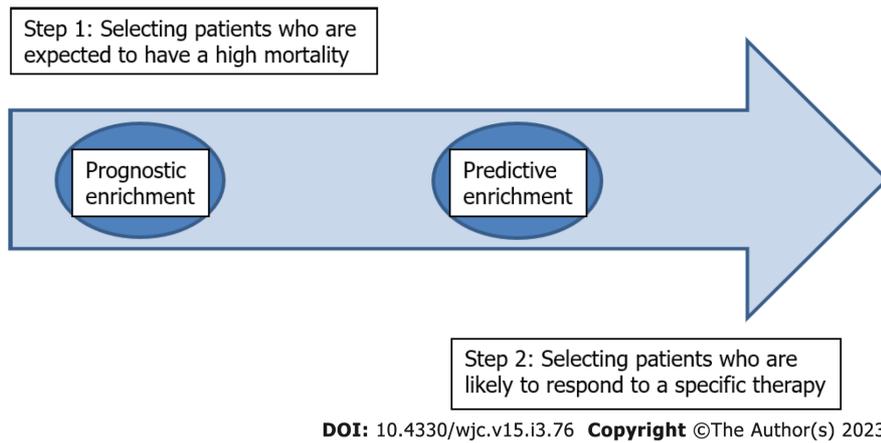


Figure 1 The path to precision medicine through patient phenotypes.

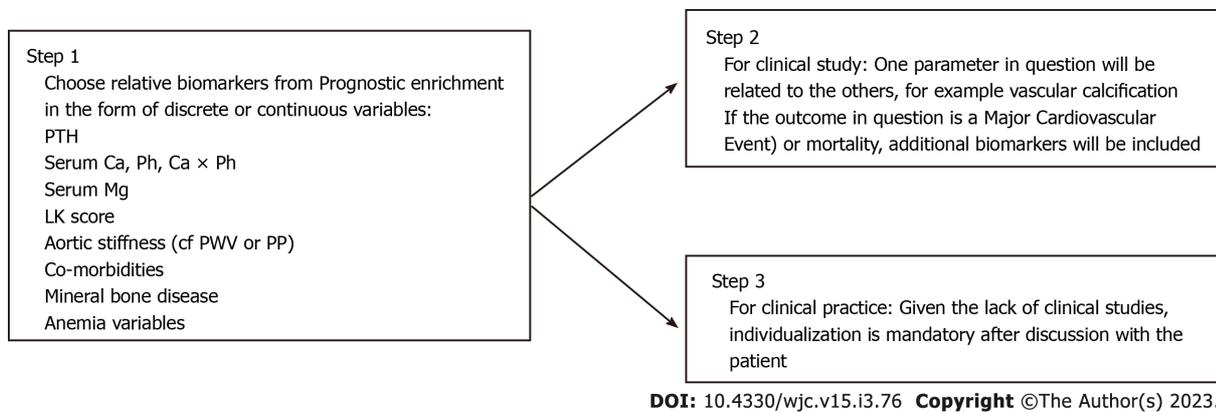


Figure 2 Predictive enrichment. Example for clinical study and clinical practice. Clinical question: Vascular disease management in CKD-5D. Bibliography: The calcification outcome in renal disease study[50] concluded that Leena Kauppila (LK) score > 4 and carotid femoral pulse wave velocity > 12 are predictors of mortality. In non-calcifiers (LK < 4) aortic stiffness plays a major role. CKD-5D: Chronic kidney disease stage 5 dialysis; PWV: Pulse wave velocity; LK: Leena Kauppila score; PTH: Parathormone; Ca: Calcium; Ph: Phosphorus; Mg: Magnesium; PP: Pulse pressure.

two strong independent predictors of CV mortality, as serum magnesium (sMg)[53] in combination with abdominal aortic calcification (AAC). We have shown that in peritoneal dialysis patients with AAC in the higher tertile of the baseline distribution, sMg levels were not predictive of outcome[54].

Erythropoietin stimulating agents have revolutionized the treatment of CKD related anemia in the last decades. Hypoxia inducible factor poly(1)-hydroxylase inhibitors (HIF-PHIs) promote erythropoietin transcription and synthesis in the liver/kidney. INNO2VATE trials have proven the non-inferiority of vadadustat compared with darbopoetin - alfa concerning the cardiovascular safety[55]. However there are long-term safety concerns related to HIF pathway interactions involving tumor growth, diabetic retinopathy, and or CKD progression. Till now no HIF-PHI is licensed for the treatment of CKD-anemia within the European Union.

Considering erythropoietin use in CKD population a U-shaped effect exists[56]. The optimal erythropoietin dose to achieve the desired level of hemoglobin (10-11.5 g/dL) for the individual patient is not known and is almost always a matter of individual assessment. Furthermore, assays detecting markers of inflammation (*e.g.*, hepcidin) which would predict clinical response in anemia lack in everyday clinical use.

CONCLUSION

In the stagnant era of effective treatment in the vulnerable population of CKD for CV morbidity and mortality, a paradigm shift seems mandatory. It is time to search for specific “biomarkers” to identify those at risk and even more those that would benefit from a targeted intervention. It is time to apply precision medicine through patient phenotypes.

FOOTNOTES

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