

Global spotlights

Use of chronic kidney disease blind spot to prevent cardiorenal outcomes

Luis M. Ruilope^{1,2,3*}, Gema Ruiz-Hurtado^{1,2*}, Blanca Miranda⁴, and Alberto Ortiz⁵

¹Cardiorenal Translational Laboratory, Institute of Research i+12, Hospital Universitario, 12 de Octubre, Avenida de Córdoba s/n, Madrid 28041, Spain; ²CIBER-CV, Hospital Universitario, 12 de Octubre, Madrid, Spain; ³School of Doctoral Studies and Research, European University of Madrid, Madrid, Spain; ⁴Renal Foundation Íñigo Álvarez de Toledo (FRIAT), Madrid, Spain; and ⁵Research Institute-Fundación Jiménez Díaz, Autónoma University, REDINREN, Madrid, Spain

Chronic kidney disease (CKD) is one of the fastest growing causes of death, predicted to become the fifth global cause of death by 2040 and the second before the end of the century in some countries where longer lifespan.¹ CKD and arterial hypertension are intimately ligated and blood pressure (BP) elevates in parallel with the progressive decay of renal function.² The diagnosis of CKD requires the demonstration of pathological albuminuria and/or an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m², albeit the concept of mildly decreased renal function (60–90 mL/min/1.73 m²) is recognized by KDIGO Guidelines.²

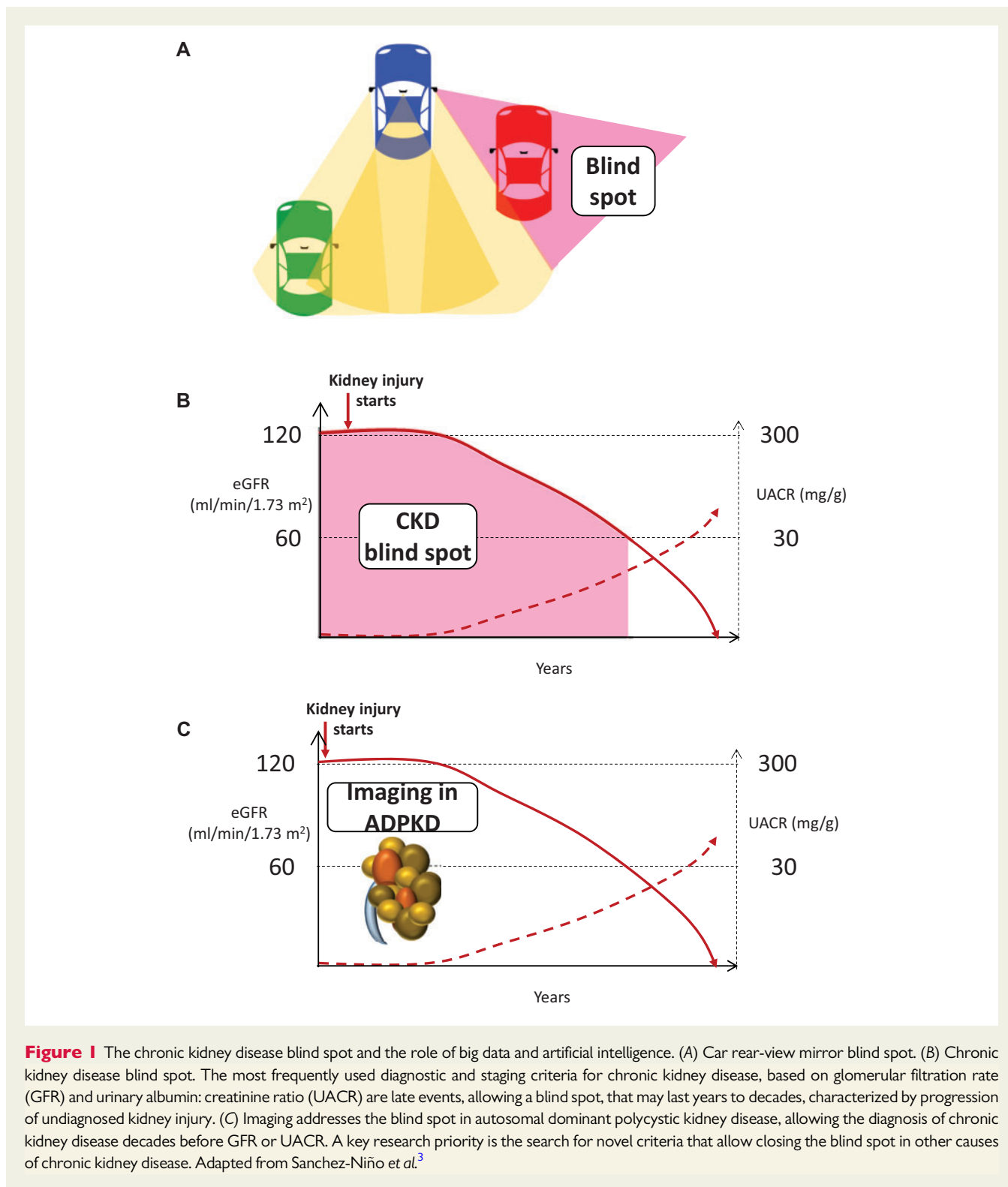
The elevation in BP must be counteracted to avoid an accelerated decay in renal function usually accompanied by a more rapid progression of the cardiovascular disease accompanying CKD. Before any of the parameters defining CKD (albuminuria or decreased eGFR) attains the threshold to diagnose the patient as having CKD, the presence of early kidney damage is a real situation not well recognized nor treated in clinical practice. In this regard, an eGFR <60 mL/min/1.73 m² implies that $>50\%$ of the functioning kidney mass has been lost. Thus, the process of kidney damage starts well before, even decades before a diagnosis of CKD is made. The obvious implication is that CKD is being diagnosed and treated late. KDIGO tried to limit the negative consequences of a delayed diagnosis by setting diagnostic criteria that involve evidence of kidney damage, such as albuminuria or imaging, even when kidney function was preserved.² However, as defined by KDIGO, pathological albuminuria is still a late event that maybe absent until late in the course of CKD. In polycystic kidney disease, imaging may allow a diagnosis of CKD several decades earlier than albuminuria or eGFR criteria. This illustrates a concept, the so-called CKD blind spot, similar to the rear-view mirror blind spot in cars: CKD is present, but we lack the tools necessary to diagnose it until later on, losing precious time needed for earlier and more effective therapy (Figure 1A–C).³ Thus, diagnostic tests should be developed that identify CKD from different causes as early as imaging does in polycystic kidney disease.

The presence of high-normal albuminuria,⁴ and the existence of a fall in eGFR ≥ 5 mL/min/year² are parameters indicating the existence of early kidney damage albeit better indicators are required. Work is ongoing on the identification of earlier biomarkers of CKD, mainly through the analysis of urine that is thought to be able to represent early kidney events better than plasma or serum.⁵ However, the most promising biomarkers imply expensive techniques that will not be routine in the clinic until cost decreases dramatically. An alternative is to use already existing clinical and laboratory data to identify early CKD or persons at risk of progression to CKD. The recent development of risk prediction equations from >5 million individuals in 34 multinational cohorts has shown high discrimination and variable calibration in diverse populations.⁶ Two formulas are being considered, one to calculate the probability of incident eGFR <60 mL/min/1.73 m² and the second to define the time to kidney failure. Further study is needed to determine whether the use of these equations improves patient outcomes, but probably the most adequate way to detect early kidney damage and to predict the evolution of CKD will be obtained by using big data and its complementary tools like machine and deep learning (Figure 2).

Human ageing is associated with progressive loss of nephrons and eGFR. This may be intimately related to the occurrence of hypertension as in a German necropsy study of young persons that died in accidents, individuals with primary hypertension had roughly half the number of nephrons than those without hypertension.⁷ A low nephron number may be congenital, as a consequence of genetic factors, low birth weight or prematurity, or acquired. Individuals with a clinical history of preterm births and low body weight at birth that frequently go together are at risk of earlier development of CKD where the risk is secondary to a decreased nephron number⁸ which facilitates the development of albuminuria and of high BP. Later on, the usual cardiovascular risk factors and the coexistence of obesity, hypertension and diabetes facilitate the progression of CKD and simultaneous

* Corresponding authors. Email: ruilope@icloud.com (L.M.R.); Tel: +34 91 3908001. Email: gema.ruiz@h12o.es (G.R.-H.)

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author(s) 2021. For permissions, please email: journals.permissions@oup.com.



cardiovascular disease.¹ Age, race, gender and genetics contribute to increase the risk of CKD together with the existence of primary renal disease (Figure 2).

The goal of BP control in CKD differs in the American and European Hypertension Guidelines and the KDIGO Guidelines⁹ that recently proposed a systolic BP target of <120 mmHg in most

subpopulations of people with CKD. More clinical trials looking jointly to cardiovascular, renal, cognitive and mortality outcomes are needed but the recommendation of the US Preventive Task Forces of screening for high BP adults aged 18 years or older¹⁰ will facilitate, through an adequate control of BP, the simultaneous prevention of renal and cardiovascular disease from the early stages of both processes.

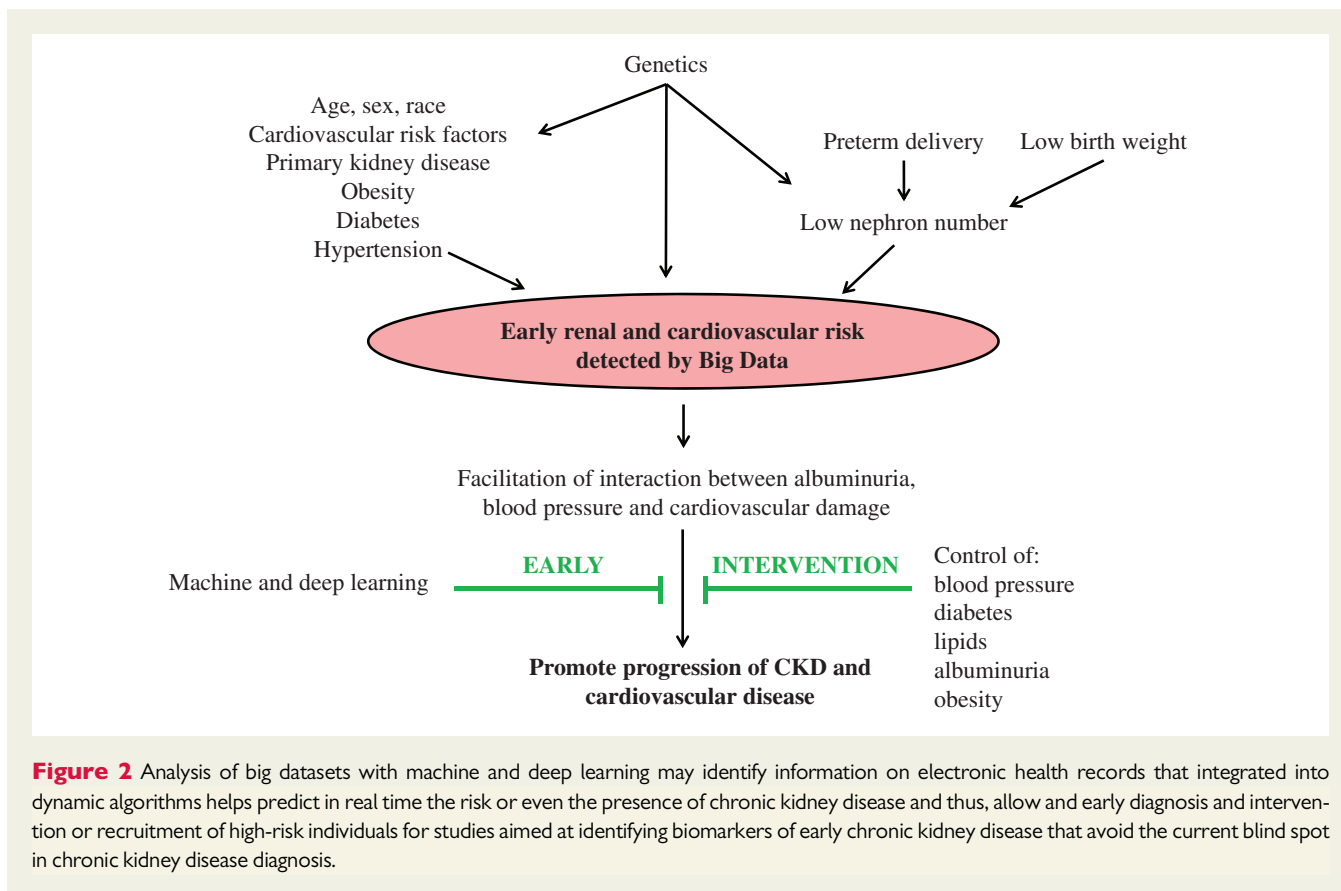


Figure 2 Analysis of big datasets with machine and deep learning may identify information on electronic health records that integrated into dynamic algorithms helps predict in real time the risk or even the presence of chronic kidney disease and thus, allow an early diagnosis and intervention or recruitment of high-risk individuals for studies aimed at identifying biomarkers of early chronic kidney disease that avoid the current blind spot in chronic kidney disease diagnosis.

Finally, once we know the content of CKD blind spot, the data of out of office BP that will be more used in the near future will contribute to better identify elevated BP at early stages of CKD. Besides hypertension, higher degrees of albuminuria and sodium intake associate with accelerated decline of eGFR rate regardless the primary cause of renal damage.² Hence, the use of antihypertensive drugs with anti-proteinuric effect, the control of dietary salt and or the use of diuretics are particularly recommended even in the absence of hypertension.

Funding

This study was supported by Instituto de Salud Carlos III FIS/Fondos FEDER (PI17/01093, PI17/01193, CP15/00129, CPII20/00022, PI18/01366, PI19/00588, PI19/00815, PI20/00763, DTS18/00032), ERA-PerMed-JTC2018 (KIDNEY ATTACK AC18/00064 and PERSTIGAN AC18/00071, ISCI-RETIC REDinREN RD016/0009), Sociedad Española de Nefrología, FRIAT, Comunidad de Madrid en Biomedicina B2017/BMD-3686 CIFRA2-CM.

Conflict of interest: A.O. has received consultancy or speaker fees or travel support from Astellas, Astrazeneca, Amicus, Amgen, Fresenius Medical Care, Bayer, Sanofi-Genzyme, Menarini, Kyowa Kirin, Alexion, Otsuka, and Vifor Fresenius Medical Care Renal Pharma and is a Director of the Catedra Mundipharma-UAM of diabetic kidney disease and the Catedra Astrazeneca-UAM of chronic kidney disease and electrolytes.

References

- Foreman KJ, Marquez N, Dolgert A, Fukutaki K, Fullman N, McGaughey M, Pletcher MA, Smith AE, Tang K, Yuan CW, Brown JC, Friedman J, He J, Heuton KR, Holmberg M, Patel DJ, Reidy P, Carter A, Cercy K, Chapin A, Douwes-Schultz D, Frank T, Goettsch F, Liu PY, Nandakumar V, Reitsma MB, Reuter V, Sadat N, Sorensen RJD, Srinivasan V, Updike RL, York H, Lopez AD, Lozano R, Lim SS, Mokdad AH, Vollset SE, Murray CJL. Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016-40 for 195 countries and territories. *Lancet* 2018;**392**:2052–2090.
- Stevens PE, Levin A; Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group Members. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. *Ann Intern Med* 2013;**158**:825–830.
- Sanchez-Niño MD, Sanz AB, Ramos AM, Fernandez-Fernandez B, Ortiz A. Clinical proteomics in kidney disease as an exponential technology: heading towards the disruptive phase. *Clin Kidney J* 2017;**10**:188–191.
- Okubo A, Nakashima A, Doi S, Doi T, Ueno T, Maeda K, Tamura R, Yamane K, Masaki T. High-normal albuminuria is strongly associated with incident chronic kidney disease in a nondiabetic population with normal range of albuminuria and normal kidney function. *Clin Exp Nephrol* 2020;**24**:435–443.
- Toft N, Lindhardt M, Adamova K, Bakker SJL, Beige J, Beulens JWJ, Birkenfeld AL, Currie G, Delles C, Dimos I, Francová L, Fridodt-Møller M, Girman P, Göke R, Havrdova T, Heerspink HJL, Kooy A, Laverman GD, Mischak H, Navis G, Nijpels G, Noutsou M, Ortiz A, Parvanova A, Persson F, Petrie JR, Ruggenti PL, Rutters F, Rychlík I, Siwy J, Spasovski G, Speeckaert M, Trillini M, Zúrbig P, von der Leyen H, Rossing P, Zimmermann S, Rädisch B, Hävemeier A, Busmann A, Wittkop U, Neuhaus B, Ax-Smolarski R, Zieglschmid V, Bollweber E, Wölk H, Curovic VR, Tougaard NH, Eickhoff MK, Pilemann-Lyberg S, Winther SA, Rosenlund SV, Hansen TW, von Scholten BJ, Hansen CS, Zobel EH, Laursen JC, Theilade S, Jelstrup L, Juhl TR, Riis D, Hermann JA, Lundgaard AG, Halkjær MLD, Aabo L, Frost Lerche T, Lajer M, Stefansen RJ, Campbell MA, Durban A, Raad J, Prigge M, Schieman M, Wilson R, Kean S, Douglas E, Surtees P, Gant C, Yeung SMH, Hagedoorn I, Flynn J, Galloway J, Brooksbank K, Aparicio C, Iliev IP, Nones F, Lo Bue F, Melacini D, Cugini D, Prandini S, Lecchi V, Yakymchuk S, Gherardi G, Villa A, Villa D, Gaspari F, Cannata AN, Ferrari S, Stucchi N, Albrechtová Š, Eldeik E, Amanaki R, Fernandez-Fernandez B, Sanchez-Rodriguez J, Vázquez C, Sanz AB, Sanchez-Niño MD, Ramos AM, Gonzalo MÁ, Schmidt U, Selim G, Gjorgovski T, Stratova SS, Stojceva-Taneva O, Schutten-Westerneng P, Wierbos B, Huvers F, De Bruin AK, Lapauw B, de Man E, Rokegem K, Inion S, Kreuzmann K, Dewettinck I, Boukens-de Graaf C, Clerc-de Jong F, Entius J, Nannings M, van Steenderen S, Petry FW, Kilic C; for the PRIORITY investigators. Early detection

- of diabetic kidney disease by urinary proteomics and subsequent intervention with spironolactone to delay progression (PRIORITY): a prospective observational study and embedded randomised placebo-controlled trial. *Lancet Diabetes Endocrinol* 2020;**8**:301–312.
6. Nelson RG, Grams ME, Ballew SH, Sang Y, Azizi F, Chadban SJ, Chaker L, Dunning SC, Fox C, Hirakawa Y, Iseki K, Ix J, Jafar TH, Köttgen A, Naimark DMJ, Ohkubo T, Prescott GJ, Rebholz CM, Sabanayagam C, Sairenchi T, Schöttker B, Shibagaki Y, Tonelli M, Zhang L, Gansevoort RT, Matsushita K, Woodward M, Coresh J, Shalev V; for the CKD Prognosis Consortium. Development of risk prediction equations for incident chronic kidney disease. *JAMA* 2019;**322**:2104.
 7. Keller G, Zimmer G, Mall G, Ritz E, Amann K. Nephron number in patients with primary hypertension. *N Engl J Med* 2003;**348**:101–108.
 8. Bertram JF, Douglas-Denton RN, Diouf B, Hughson MD, Hoy WE. Human nephron number: implications for health and disease. *Pediatr Nephrol* 2011;**26**:1529–1533.
 9. Cheung AK, Chang TI, Cushman WC, Furth SL, Hou FF, Ix JH, Knoll GA, Muntner P, Pecoits-Filho R, Sarnak MJ, Tobe SW, Tomson CRV, Lytvyn L, Craig JC, Tunnicliffe DJ, Howell M, Tonelli M, Cheung M, Earley A, Mann JFE. Executive summary of the KDIGO 2021 clinical practice guideline for the management of blood pressure in chronic kidney disease. *Kidney Int* 2021;**99**:559–569.
 10. Krist AH, Davidson KW, Mangione CM, Cabana M, Caughey AB, Davis EM, Donahue KE, Doubeni CA, Kubik M, Li L, Ogedegbe G, Pbert L, Silverstein M, Stevermer J, Tseng CW, Wong JB; Force UPST. Screening for hypertension in adults: US Preventive Services Task Force Reaffirmation Recommendation Statement. *JAMA* 2021;**325**:1650–1656.