


# Chronic kidney disease: Definition, updated epidemiology, staging, and mechanisms of increased cardiovascular risk

Scott Wilson BA<sup>1,2</sup> | Pasquale Mone MD<sup>3,4</sup> | Stanislovas S. Jankauskas PhD<sup>1,2</sup> |  
Jessica Gambardella PhD<sup>1,2,5</sup> | Gaetano Santulli MD, PhD<sup>1,2,5</sup> 

<sup>1</sup>Department of Medicine, Wilf Family Cardiovascular Research Institute, Einstein Institute for Aging Research, Albert Einstein College of Medicine, New York, NY, USA

<sup>2</sup>Department of Molecular Pharmacology, Einstein-Mount Sinai Diabetes Research Center (ES-DRC), Fleischer Institute for Diabetes and Metabolism (FIDAM), Albert Einstein College of Medicine, New York, NY, USA

<sup>3</sup>University of Campania "Luigi Vanvitelli", Naples, Italy

<sup>4</sup>ASL Avellino, Avellino, Italy

<sup>5</sup>Department of Advanced Biomedical Science, International Translational Research and Medical Education Consortium (ITME), "Federico II" University, Naples, Italy

**Correspondence:** Prof. Gaetano Santulli, Department of Medicine, Wilf Family Cardiovascular Research Institute, Einstein Institute for Aging Research, Albert Einstein College of Medicine, New York, NY 10461, USA and Department of Advanced Biomedical Science, International Translational Research and Medical Education Consortium (ITME) "Federico II" University, Naples 80131, Italy.

Email: gsantulli001@gmail.com

## Funding information

The Santulli's Laboratory is supported in part by the National Institutes of Health (NIH): National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK: R01-DK123259, R01-DK033823, R00-DK107895), National Heart, Lung, and Blood Institute (NHLBI: R01-HL146691, T32-HL144456), National Institute on Aging (NIA: R56-AG066431) to G.S. and by the American Heart Association (AHA-20POST35211151 to J.G.).

Chronic kidney disease (CKD) is a heterogeneous group of disorders that manifest in various ways depending upon the severity of disease and the underlying cause(s).<sup>1</sup>

## 1 | CKD: DEFINITION

Chronic kidney disease is defined by the presence of kidney damage or decreased kidney function for at least three months, irrespective of the cause.<sup>2</sup> Kidney damage generally refers to pathologic anomalies in the native or transplanted kidney, established via imaging, biopsy, or deduced from clinical markers like increased albuminuria—*that is*, albumin-to-creatinine ratio (ACR) >30 mg/g (3.4 mg/mMol)—or urinary sediment alterations; decreased kidney function refers to a reduced glomerular filtration rate (GFR), which is usually estimated (eGFR) from the serum concentration of creatinine.<sup>3</sup>

## 2 | UPDATED CKD EPIDEMIOLOGY

According to the US Centers for Disease Control and Prevention (CDC), ~37 million people in the United States—~15% of adults—are estimated to have CKD. Of note, 90% of adults with CKD do not know they have it and 1 in 2 people with very low kidney function who are not on dialysis are not aware of the fact that they have CKD.<sup>4</sup> Diabetes and hypertension are the major causes of CKD in adults: According to the CDC, 1 in 3 adults with diabetes and 1 in 5 adults with hypertension may have CKD. According to the current CDC statistics, CKD is more common in people aged 65 years or older (38%) than in people aged 45-64 years (13%) or 18-44 years (7%), and is slightly more common in women (15%) than men (12%); moreover, African Americans are about 3 times more likely than whites to develop ESKD.<sup>5</sup>

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2021 The Authors. *The Journal of Clinical Hypertension* published by Wiley Periodicals LLC.

### 3 | MECHANISMS LEADING TO CKD

In the Western world, the main risk factor for CKD development is diabetes, which is present in 30%–50% of CKD patients.<sup>6</sup> Hypertension and smoking are other strong factors increasing the risk of CKD as well as the speed of its progression.<sup>6</sup> Instead, in India, Asia, and Sub-Saharan Africa, the leading cause of CKD is glomerulonephritis, followed by CKD of unknown genesis, probably prompted by soil pollution with heavy metals and pesticides and excessive use of herbal-based traditional medicines.<sup>7</sup> HIV contributes significantly to CKD due to the direct glomerular interstitial damage caused by HIV per se and to the significant nephrotoxicity of antiretroviral therapies.<sup>6</sup>

Despite the diverse etiologies, the main mechanism of CKD is believed to heavily rely on microvasculature dysfunction. Indeed, hypertension, dyslipidemia, and smoking act on the endothelium in glomeruli and interstitium, eventually resulting in the infiltration of macrophages and other inflammatory cells.<sup>6</sup> Macrophages activate mesangial cells in glomeruli, facilitating their expansion and extracellular matrix production, which results in substitution of capillaries with matrix, thus reducing the surface through which the blood filtration occurs resulting in a net filtration decrease and accumulation of uremic toxins.<sup>8</sup> At the same time, glomerulosclerosis is accompanied by dysfunction of podocytes, cells playing a central role in the proper function of the glomerular filtration barrier. As a result, proteinuria develops and tubular epithelium becomes exposed to proteins such as albumin, complement system components, and cytokines which further exacerbate the inflammatory response.<sup>8</sup> Accumulation of damaged DNA in tubular epithelium through the chronic inflammation produces cell cycle arrest, accompanied by a switch to a specific type of secretory phenotype, which further facilitates pro-fibrotic modifications.<sup>8</sup> Uncontrolled accumulation of extracellular matrix decreases the capillary density, thus obstructing oxygen and nutrient supply to tubular cells. Eventually, the kidney tissue ends up with tubular atrophy and ubiquitous fibrosis.

### 4 | CKD AND CARDIOVASCULAR DISEASE

The classification and staging of CKD are based on the cause(s), on the level of albuminuria, and on glomerular filtration rate (GFR).<sup>2</sup> Kidney failure represents the end stage of CKD (ESKD: end-stage kidney disease) and is defined as severely reduced kidney function or treatment with dialysis. CKD has been shown to lead to an increased risk for cardiovascular diseases, and cardiovascular complications remain the most common cause of death and disability in CKD patients.<sup>9</sup> Even with a normal eGFR, patients with ACR > 30 mg/g have a significantly increased risk for all-cause and cardiovascular mortality, compared to subjects with a lower ACR.<sup>10</sup>

Vascular alterations reflect kidney dysfunction in CKD subjects, and arterial stiffness is considered one of its most common markers.<sup>11</sup> Arterial stiffness, characterized by a gradual degradation of the elastic lamellae within the vascular media alongside structural

changes in collagen cross-linking and calcification, is present in several cardiovascular and renal diseases, resulting in the reduced ability of arteries to respond to changes in blood pressure. In the current issue of the Journal, Guo and colleagues examined different parameters of arterial stiffness in CKD patients, proposing the 24-hour mean pulse pressure (PP) as the best marker to predict renal outcomes.<sup>12</sup>

### 5 | MECHANISMS UNDERLYING ARTERIAL STIFFNESS

Overall, arterial stiffness is a sign of structural and functional modifications of the vascular wall that eventually lead to organ damage. There are 2 main hemodynamic parameters of pressure and flow: a steady component and a pulsatile component. The first one is represented by mean arterial pressure (MAP), the product of cardiac output by vascular resistance, which is generally measured in hypertensive subjects. The second one is represented by the PP, which is mainly determined by stroke volume, aortic stiffness, and wave reflections. As confirmed by Guo and collaborators, PP is a useful parameter to evaluate arterial stiffness.<sup>12</sup> PP is divided into brachial PP and central PP; the difference between these two components is defined PP amplification and it is approximately 14 mmHg. PP amplification might be superior than PP to detect arterial stiffness in CKD patients, particularly in elderly populations.<sup>13</sup>

In patients with ESKD undergoing hemodialysis, clinical studies have shown that BP is frequently associated with an increase in systolic BP (SBP) alone, with normal or even low diastolic BP (DBP). These aspects could impact arterial stiffness because they are associated with increased stiffness of large conduit arteries and early wave reflections; importantly, an increased stiffness has been shown to be independent of MAP.<sup>14</sup>

In this context, pulse wave velocity (PWV) remains a widely used marker to evaluate arterial stiffness. PWV represents the pressure generated by the ventricular contraction along the aorta.<sup>13,15</sup> Since pulse waves travel faster in stiffer arteries, arterial stiffness augments PWV, with normal values ranging between 3 and 5 m/s in young people but commonly increase with age.

Chronic kidney disease and creatinine levels are among the most critical determinants of PWV increase; in this scenario, a significant relationship has been observed between GFR reduction, proteinuria, and an increase in carotid-femoral PWV.<sup>16</sup> Analyzing aortic PWV in 101 living kidney donors and their 101 corresponding recipients, Bahous and collaborators found that the major parameters associated with PWV were time since nephrectomy (donation date) in donors and renal rejection in recipients; additionally, plasma creatinine doubling secondary to chronic allograft nephropathy was significantly associated both to renal rejection and to donor PWV, independent of age.<sup>17</sup>

Several studies have demonstrated that an optimal control of blood pressure can prevent arterial stiffness.<sup>18–20</sup> Furthermore, in 2005 Wang and coworkers demonstrated that a stepwise increase

in arterial stiffness reflects the stage of CKD<sup>21</sup>; in this study, a greater PWV was observed in patients with more advanced CKD from stages 1 to 5; SBP and the estimated GFR per 1.73 m<sup>2</sup> were the major clinical determinants of arterial stiffness in patients with CKD independent of conventional risk factors for cardiovascular diseases.<sup>21</sup>

## 6 | HOW TO QUANTIFY ARTERIAL STIFFNESS?

Arterial stiffness is commonly measured by PWV, which, as mentioned above, refers to the speed of a pressure wave's propagation across an arterial tree. With age, arterial walls become less distensible, leading to increased PWV. Carotid-femoral pulse wave velocity (cfPWV) is a well-validated measure of aortic stiffness that predicts the likelihood of future cardiovascular events. Indeed, cfPWV can predict future cardiovascular disease independently from conventional atherosclerotic risk factors (sex, age, smoking status, systolic blood pressure, dyslipidemia, and diabetes) in patients with ESKD.<sup>22</sup> The cfPWV threshold of 10m/s, established by the 2013 European Society of Hypertension Guidelines,<sup>23</sup> is generally agreed upon as an indication of asymptomatic hypertension-mediated organ damage. cfPWV is measured by timing the movement of a pressure wave between the carotid and femoral arteries. Compared to peripheral measurements of PWV, cfPWV is more useful since central arteries appear most susceptible to age-related stiffening.<sup>24</sup> Additionally, brachial-ankle pulse wave velocity (baPWV) has been proposed as an alternate measure of arterial stiffness as a wider screening tool since it is easier and more convenient to conduct clinically. Other parameters to measure arterial stiffness include the augmentation index at heart rate 75 bpm (Alx@75)<sup>25</sup> and the ambulatory arterial stiffness index.<sup>26</sup>

Changes in arterial stiffness may be hastened in hypertensive patients whose treatments fail to reduce their PWV. Moreover, failure to reduce PWV in hypertensive patients was a significant predictor of cardiovascular death in ESKD despite reasonable blood pressure control.<sup>27</sup>

There is conflicting evidence that early atherosclerosis is linked to increased arterial stiffness. However, large arterial calcification present in advanced atherosclerosis is associated with increased PWV in CKD and ESKD.<sup>28</sup> This association may be more related to the plaque's contents (*i.e.*, degree of calcification) than its size.<sup>29,30</sup> There are several direct hemodynamic consequences of increased PWV. For one, age-related widening of PP—the difference between systolic and diastolic blood pressure—is partly determined by arterial stiffening. Furthermore, arterial stiffening is linked to wave reflection arriving earlier at the aorta during systole due to increased PWV, likely affecting central PP. This aspect is significant since higher central PP results in increased left ventricular afterload, predisposition for ventricular hypertrophy, and decreased coronary blood flow.

## CONFLICT OF INTEREST

None.

## ORCID

Gaetano Santulli  <https://orcid.org/0000-0001-7231-375X>

## REFERENCES

1. Wanner C, Lopau K. What Is the Utility of KDIGO Criteria to Identify High-Risk Populations? *Am J Kidney Dis.* 2021;77(1):7-8.
2. Levey AS, Eckardt K-U, Dorman NM, et al. Nomenclature for kidney function and disease: report of a Kidney Disease: Improving Global Outcomes (KDIGO) Consensus Conference. *Kidney Int.* 2020;97(6):1117-1129.
3. Navaneethan SD, Zoungas S, Caramori ML, et al. Diabetes management in chronic kidney disease: synopsis of the 2020 KDIGO clinical practice guideline. *Ann Intern Med.* 2020, In press.
4. Schrauben SJ, Chen H-Y, Lin E, et al. Hospitalizations among adults with chronic kidney disease in the United States: A cohort study. *PLoS Med.* 2020;17(12):e1003470.
5. Vart P, Powe NR, McCulloch CE, et al. National trends in the prevalence of chronic kidney disease among Racial/Ethnic and Socioeconomic Status Groups, 1988–2016. *JAMA Netw Open.* 2020;3(7):e207932.
6. Webster AC, Nagler EV, Morton RL, Masson P. Chronic kidney disease. *Lancet.* 2017;389(10075):1238-1252.
7. Fitria L, Prihartono NA, Ramdhan DH, Wahyono TYM, Kongtip P, Woskie S. Environmental and occupational risk factors associated with chronic kidney disease of unknown etiology in west javanese rice farmers, Indonesia. *Int J Environ Res Public Health.* 2020;17(12):4521.
8. Humphreys BD. Mechanisms of renal fibrosis. *Annu Rev Physiol.* 2018;80:309-326.
9. Druke TB, Floege J. Cardiovascular complications of chronic kidney disease: pioneering studies. *Kidney Int.* 2020;98(3):522-526.
10. van der Velde M, Matsushita K, Coresh J, et al. Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. A collaborative meta-analysis of high-risk population cohorts. *Kidney Int.* 2011;79(12):1341-1352.
11. Hoshida S, Suzuki D, Kario K. Circadian variation and arterial stiffness in chronic kidney disease and their treatment. *Am J Hypertens.* 2020, In press.
12. Guo X, Li Y, Yang Y, et al. Noninvasive markers of arterial stiffness and renal outcomes in patients with chronic kidney disease. *J Clin Hypertens (Greenwich).* 2020, In press.
13. Avolio AP, Van Bortel LM, Boutouyrie P, et al. Role of pulse pressure amplification in arterial hypertension: experts' opinion and review of the data. *Hypertension.* 2009;54(2):375-383.
14. Salvi P, Parati G. Chronic kidney disease: Arterial stiffness and renal function—a complex relationship. *Nat Rev Nephrol.* 2015;11(1):11-13.
15. Lanni F, Santulli G, Izzo R, et al. The PI(A1/A2) polymorphism of glycoprotein IIIa and cerebrovascular events in hypertension: increased risk of ischemic stroke in high-risk patients. *J Hypertens.* 2007;25(3):551-556.
16. Gosse P, Safar ME. Arterial stiffness and plasma creatinine in untreated hypertensive patients. *Am J Hypertens.* 2005;18(9 Pt 1):1140-1145.
17. Bahous SA, Stephan A, Blacher J, Safar ME. Aortic stiffness, living donors, and renal transplantation. *Hypertension.* 2006;47(2):216-221.
18. Liew Y, Rafey MA, Allam S, Arragain S, Butler R, Schreiber M. Blood pressure goals and arterial stiffness in chronic kidney disease. *J Clin Hypertens (Greenwich).* 2009;11(4):201-206.

19. Balta S, Kucuk U, Demirkol S, Demir M, Ozturk C. Arterial stiffness parameters in patients with chronic kidney disease. *J Clin Hypertens (Greenwich)*. 2014;16(2):157.
20. Lilitkarntakul P, Dhaun N, Melville V, et al. Blood pressure and not uraemia is the major determinant of arterial stiffness and endothelial dysfunction in patients with chronic kidney disease and minimal co-morbidity. *Atherosclerosis*. 2011;216(1):217-225.
21. Wang MC, Tsai WC, Chen JY, Huang JJ. Stepwise increase in arterial stiffness corresponding with the stages of chronic kidney disease. *Am J Kidney Dis*. 2005;45(3):494-501.
22. Ben-Shlomo Y, Spears M, Boustred C, et al. Aortic pulse wave velocity improves cardiovascular event prediction: an individual participant meta-analysis of prospective observational data from 17,635 subjects. *J Am Coll Cardiol*. 2014;63(7):636-646.
23. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J*. 2013;34(28):2159-2219.
24. Mitchell GF, Parise H, Benjamin EJ, et al. Changes in arterial stiffness and wave reflection with advancing age in healthy men and women: the Framingham Heart Study. *Hypertension*. 2004;43(6):1239-1245.
25. Nelson MR, Stepanek J, Cevette M, Covalciuc M, Hurst RT, Tajik AJ. Noninvasive measurement of central vascular pressures with arterial tonometry: clinical revival of the pulse pressure waveform? *Mayo Clin Proc*. 2010;85(5):460-472.
26. Dolan E, Thijs L, Li Y, et al. Ambulatory arterial stiffness index as a predictor of cardiovascular mortality in the Dublin Outcome Study. *Hypertension*. 2006;47(3):365-370.
27. Townsend RR, Anderson AH, Chirinos JA, et al. Association of pulse wave velocity with chronic kidney disease progression and mortality: findings from the CRIC study (Chronic Renal Insufficiency Cohort). *Hypertension*. 2018;71(6):1101-1107.
28. Haydar AA, Covic A, Colhoun H, Rubens M, Goldsmith DJ. Coronary artery calcification and aortic pulse wave velocity in chronic kidney disease patients. *Kidney Int*. 2004;65(5):1790-1794.
29. Gambardella J, Wang X, Mone P, Khondkar W, Santulli G. Genetics of adrenergic signaling drives coronary artery calcification. *Atherosclerosis*. 2020;310:88-90.
30. Cecelja M, Hussain T, Greil G, et al. Multimodality imaging of subclinical aortic atherosclerosis: relation of aortic stiffness to calcification and plaque in female twins. *Hypertension*. 2013;61(3):609-614.

**How to cite this article:** Wilson S, Mone P, Jankauskas SS, Gambardella J, Santulli G. Chronic kidney disease: Definition, updated epidemiology, staging, and mechanisms of increased cardiovascular risk. *J Clin Hypertens*. 2021;00:1-4. <https://doi.org/10.1111/jch.14186>