Cardiovascular complications of chronic kidney disease: pioneering studies

Kidney International (2020) **98,** 522–526; https://doi.org/10.1016/j.kint.2020.07.001

KEYWORDS: anemia; cardiac ischemia; cardiovascular disease; chronic kidney disease; dialysis; myocardial fibrosis; vascular calcification; vascular stiffness

Tilman B. Drüeke[1] and Jürgen Floege[2]

[1]*Inserm U-1018, CESP, Paris-Ile-de-France-Ouest University (UVSQ), Paris-Sud University (UPS), and Paris Saclay University, Villejuif, France; and* [2]*Department of Nephrology and Clinical Immunology, University Hospital, Rheinisch Westfälische Technische Hochschule Aachen, Aachen, Germany*

Correspondence: *Tilman B. Drüeke, Inserm Unit 1018, Team 5, CESP, hôpital Paul Brousse, 16 avenue Paul Vaillant Couturier, 94807 Villejuif Cedex, France. E-mail: tilman.drueke@inserm.fr*

Compared with the general population, patients with chronic kidney disease (CKD) suffer from a dramatic increase in cardiovascular morbidity and mortality. The incidence increases as CKD progresses. The relative increase is particularly marked in young as compared with elderly patients. Since its beginning, *Kidney International* has published numerous articles dealing with all aspects of this issue including diagnosis, pathophysiology, epidemiology, treatment, and prevention. The articles presented below have greatly contributed to a better understanding and management of cardiovascular disease in the setting of CKD.

Ischemic heart disease in patients on hemodialysis therapy

Rostand SG, Gretes JC, Kirk KA, et al. Ischemic heart disease in patients with uremia undergoing maintenance hemodialysis. Kidney Int. 1979;16:600–611.[1] The prevalence of cardiovascular disease and mortality is markedly higher in patients with CKD than in the general population.[2,3] The relative contribution of atherosclerosis to cardiovascular disease in such patients has long been a matter of debate.[4] In the early 1970s, Lindner *et al.*[5] proposed the occurrence of "accelerated atherosclerosis" in chronic hemodialysis patients. However, Rostand *et al.* subsequently questioned this hypothesis.[1] The authors examined the 6-year cumulative incidence of ischemic heart disease (IHD; angina pectoris, myocardial infarction) in 382 hemodialysis patients in Birmingham, AL. The group was relatively young (mean age, 43 years) and was distributed nearly evenly between men and women and between whites and blacks. A total of 62 patients had evidence of IHD before starting dialysis, 39 patients developed symptomatic IHD after the onset of hemodialysis, and 281 patients never exhibited IHD either before or after starting hemodialysis therapy. More than 80% of the 382 patients had risk factors of IHD including arterial hypertension and left ventricular hypertrophy (LVH). Few patients had diabetes. Information on smoking or body habitus was not available. Despite the above risk factors, only 26% of the patients exhibited signs of IHD, and only 10% developed IHD after dialysis initiation (half of them in the first year). Analysis by sex and race showed similar rates of IHD in men and women, but the rate in whites was twice that in blacks. In men, the rate was not different from nondialysis men with similar coronary risk factors, whereas in women, the rate was twice that of nondialysis cohort. Figure 1 shows that development of IHD did not adversely affect long-term survival as compared with patients with prior evidence of IHD or those without IHD. Death from myocardial infarction occurred in 3 of 320 patients at risk. Autopsy data in 33 patients revealed 70% stenosis of coronary arteries in only 7 patients, 4 of whom had antecedent disease. Thus only 1% of the 320 patients at risk for developing *de novo* IHD died of myocardial infarction, and autopsy data did not suggest accelerated atherosclerosis. Ischemic heart damage must therefore have been due to causes other than atheromatous disease in the majority of these relatively young and mostly nondiabetic hemodialysis patients.

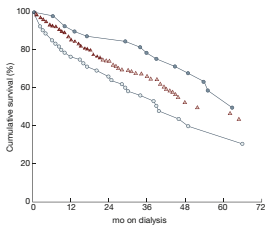

Figure 1 |

Figure 1 shows the effect of ischemic heart disease on cumulative survival of patients on maintenance hemodialysis. Open circles represent patients with IHD before onset of

Editor's Note

This article is part of the *KI* 60th anniversary series. This month's topic is related to seminal contributions to cardiovascular disease in patients with chronic kidney disease.

hemodialysis (N = 62). Closed circles are patients developing IHD after onset of hemodialysis (N = 39). Open triangles are patients exhibiting no symptoms of IHD (N = 281). Adapted with permission from Rostand SG, Gretes JC, Kirk KA, et al. Ischemic heart disease in patients with uremia undergoing maintenance hemodialysis. *Kidney Int.* 1979;16:600–611.[1] Copyright © 1979 by the International Society of Nephrology.

Uremia-associated increase in myocardial interstitial fibrosis

Mall G, Rambausek M, Neumeister A, et al. Myocardial interstitial fibrosis in experimental uremia—implications for cardiac compliance. Kidney Int. 1988;33:804–811.[6] One among several possible causes of IHD in the uremic state may be the development of myocardial fibrosis, as shown by Mall *et al.*[6] The authors used an experimental rat model of 5/6th nephrectomy to examine the effect of uremia on cardiac morphology in the presence or absence of concomitant treatment of hypertension. Blood pressure was measured by tail plethysmography, and cardiac structure by macro- and micromorphometric analyses using light and electron microscopy. At day 21, the authors observed a significant increase of total heart weight in the uremic rats compared with normal controls (1040 ± 73 vs. 871 ± 81 mg wet wt, means ±SD) with an increase of both right and left ventricular weight. This was accompanied by the reduction of capillary cross-sectional area despite unchanged capillary length. The volume density (cm^3/cm^3) of cardiomyocytes was unchanged, but volume density of interstitial tissue (excluding capillary lumen) had more than doubled. This was associated with signs of activation of interstitial cells, that is, increased volume of interstitial cell nuclei and interstitial cell cytoplasm (Figure 2) and a significant increase of noncellular interstitial ground substance. After 3 months of uremia, electron microscopy showed collagen fiber deposition in the interstitium. When 5/6th-nephrectomized rats received the angiotensin converting inhibitor ramipril, this reduced blood pressure and heart weight but not interstitial expansion compared with placebo-treated rats. Comparable interstitial myocardial fibrosis was not observed in hearts of nonuremic rats with renovascular (one clip-two kidney) hypertension. Thus, the uremic state increases myocardial fibrosis by mechanisms independent of hypertension. This finding may explain, at least partially, the observation of diastolic heart dysfunction secondary to impaired compliance in patients with CKD. Subsequently, Amann *et al.*[7] from the group of E. Ritz showed in a postmortem study of chronic hemodialysis patients that in parallel to the augmented volume density of myocardial interstitial tissue, cardiomyocyte diameter was also enlarged, whereas myocardial capillary length was reduced, resulting in "myocyte/capillary mismatch" and hence myocardial ischemia.

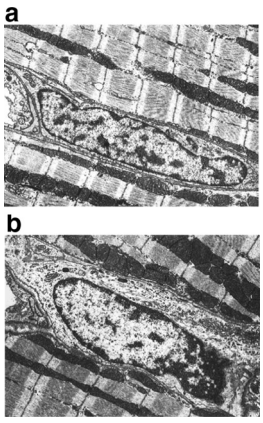

Figure 2 |

Figure 2 shows the (**a**) myocardial interstitial cell of a control animal (electron micrograph, magnification 12,100:1). Cytoplasm without evidence of cell activation. (**b**) Activated interstitial cell of a uremic rat 3 weeks after 5/6 nephrectomy (magnification 14,300:1). Note the increase in cytoplasm. Adapted with permission from Mall G, Rambausek M, Neumeister A, et al. Myocardial interstitial fibrosis in experimental uremia—implications for cardiac compliance. *Kidney Int.* 1988;33:804–811.[6] Copyright © 1988 by the International Society of Nephrology.

Aortic pulse wave velocity index and mortality in end-stage renal disease

Blacher J, Safar ME, Guerin AP, et al. Aortic pulse wave velocity index and mortality in end-stage renal disease. Kidney Int. 2003;63:1852–1860.[8] Because of the dramatic increase in cardiovascular morbidity and mortality of patients with CKD, it is of utmost importance to identify potentially reversible risk factors. The groups of London and Safar were among the first to identify an association of increased aortic pulse wave velocity (PWV) with mortality in maintenance hemodialysis patients,[8] and that survival was

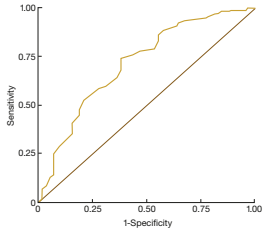

Figure 3 |

positively associated with angiotensin converting enzyme inhibitor use.[9] The aim of the present study by London *et al.* in mortality in maintenance hemodialysis patients was to examine the place of aortic stiffness relative to that of other strong predictors of mortality including age, blood pressure, heart rate, and gender.[8] They measured aortic PWV in a cohort of 242 patients using Doppler ultrasonography. Based on a nomogram established on 469 nonuremic subjects, a theoretical value of PWV was determined in mortality in maintenance hemodialysis patients according to age, blood pressure, gender, and heart period. The PWV index (measured minus theoretical PWV) was then calculated for each individual patient. Based on Cox analysis, the PWV index, but neither pulse pressure nor cardiac mass, was a strong and independent predictor of both cardiovascular and overall mortality, together with age and time on dialysis before inclusion. Patients with positive (vs. negative) PWV indices had a 2-fold adjusted risk of mortality during the follow-up. Per each 1 m/s PWV index increment, they observed a 34% (crude) and a 14% (adjusted) increase in both cardiovascular and overall mortality ($P < 0.02$ for all). The optimal cutoff value of PWV index to predict cardiovascular mortality was 1.63 m/s with 62% sensitivity, 74% specificity, 43% positive predictive value, and 86% negative predictive value (area under receiving operating characteristic curve = 0.72 ± 0.12) (Figure 3). Thus in maintenance hemodialysis patients, the PWV index provides information about cardiovascular and overall mortality risk with high predictive power, showing that PWV measurements provide discriminatory prognostic power over and above conventional cardiovascular risk factors.

Figure 3 shows receiving operating characteristic curves: pulse wave velocity index in the detection of cardiovascular and overall mortality. Area under curves, respectively, 0.72 ± 0.11. Adapted with permission from Blacher J, Safar ME, Guerin AP, et al. Aortic pulse wave velocity index and mortality in end-stage renal disease. *Kidney Int.* 2003;63:1852–1860.[8] Copyright © 2003 by the International Society of Nephrology.

Effect of anemia correction on established LVH in patients undergoing hemodialysis therapy

Foley RN, Parfrey PS, Morgan J, et al. Effect of hemoglobin levels in hemodialysis patients with asymptomatic cardiomyopathy. Kidney Int. 2000;58:1325–1335.[10] Anemia has long been known to be an important contributor to the cardiomyopathy of patients with advanced CKD, together with hypertension and volume overload.[11] An independent association of anemia with LVH was subsequently shown to also hold true for earlier stages of CKD.[12] The question then arose whether anemia correction by erythropoietin treatment might lead to a regression of LVH and cardiac dysfunction. Foley *et al.* randomly assigned 146 chronic hemodialysis patients with either concentric LVH or LV dilation to epoetin alpha designed to achieve hemoglobin levels of either 10 or 13.5 g/dl.[10] The study duration was 48 weeks. The primary outcomes were the change in LV mass index in those with concentric LVH and the change in cavity volume index in those with LV dilation. The authors found that the patients with concentric LVH had comparable changes of LV mass index, although a trend to a lesser increase over time was observed with full anemia correction (blue) compared with partial correction (red), as shown in Figure 4. In patients with overt LV dilation, full anemia correction had no beneficial echocardiographic effects either. Note that the extent of LV dilation in this group was severe. Despite these negative results, the authors speculated whether normalization of hemoglobin at earlier CKD stages might be beneficial. Another possible explanation for this negative finding is the degree of anemia at baseline. A decade earlier, London *et al.*[13] showed that erythropoietin treatment of chronic hemodialysis patients led to a decrease in LV end-diastolic diameter and mass index, together with a decrease in cardiac index and heart rate but no change in fractional ejection. In these patients, hemoglobin levels were raised from a mean of 6.8 to 10.6 g/dl, whereas in the trial by Foley *et al.* baseline hemoglobin levels were 9.5 to 10.5 g/dl. Thus, partial anemia correction in patients with kidney failure and severe anemia improves cardiac structure and function, whereas full anemia correction does not appear to provide further benefit. It has even been shown to be harmful for clinical outcomes in patients with CKD.[14]

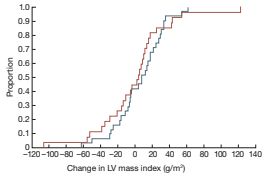

Figure 4 |

Figure 4 is adapted with permission from Foley RN, Parfrey PS, Morgan J, et al. Effect of hemoglobin levels in hemodialysis patients with asymptomatic cardiomyopathy. *Kidney*

Int. 2000;58:1325–1335.[10] Copyright © 2000 by the International Society of Nephrology.

Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients

Chertow GM, Burke SK, Raggi P, et al. Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. Kidney Int. 2002;62:245–252.[15] Cardiovascular calcification has long been recognized to be both a risk factor and a possible contributor to morbidity and mortality in patients with CKD. Its prevalence in such patients is high and is favored by an imbalance between promoting and inhibitory factors.[16] A major persistent issue is its treatment, prevention, and potential regression.[17,18] Because calcium and phosphate overload are major contributors to cardiovascular calcification in CKD, Chertow *et al.* conducted a randomized controlled trial comparing sevelamer, a calcium-free nonabsorbed polymer, with calcium-based phosphate binders in 200 prevalent chronic hemodialysis patients.[15] Study outcomes included biochemical parameters (serum phosphorus, calcium, and intact parathyroid hormone) and calcification of the coronary arteries and thoracic aorta using a calcification score derived from electron beam tomography. The authors first showed that sevelamer and calcium-containing phosphate binders provided equivalent control of serum phosphorus. Second, serum calcium concentration was significantly higher in the calcium-treated group, and hypercalcemia was 3 times more common (16% vs. 5%). Third, more subjects in the calcium group had end-of-study intact parathyroid hormone levels below the target of 150 to 300 pg/ml (57% vs. 30%). Fourth, and most importantly, at study completion, the calcium scores in the coronary arteries and aorta had increased significantly more in the calcium-treated group compared with the sevelamer-treated group. Figure 5 shows the greater increase in coronary calcification scores in the calcium group (green columns) than in the sevelamer group (orange column). Thus, sevelamer was found to protect the patients better than calcium-based phosphate binders against the progression of vascular calcification associated with CKD. These findings were subsequently questioned based on another trial, comparing sevelamer with calcium acetate plus statin administration in such patients.[19] However, patients in this latter study had a higher prevalence of diabetic nephropathy and smoking, unlikely to be affected by the choice of phosphate binders, and a much faster progression of coronary calcifications, questioning the validity of the conclusions.[20] Many other approaches to halt progress of cardiovascular calcifications in CKD have been proposed or are under investigation.[16,18]

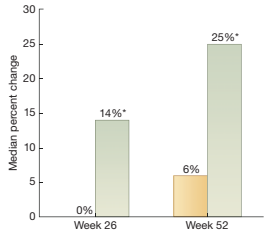

Figure 5|

Figure 5 is adapted with permission from Chertow GM, Burke SK, Raggi P, et al. Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. *Kidney Int.* 2002;62:245–252.[15] Copyright © 2002 by the International Society of Nephrology.

DISCLOSURE

TBD reports personal fees from Akebia, Amgen, Astellas, Chugai, Fresenius Medical Care, Kyowa Hakko Kirin, Sanofi, and Vifor. JF reports personal fees from Amgen, Bayer, Chugai, Fresenius Medical Care, and Vifor.

REFERENCES

1. Rostand SG, Gretes JC, Kirk KA, et al. Ischemic heart disease in patients with uremia undergoing maintenance hemodialysis. *Kidney Int*. 1979;16:600–611.
2. Go AS, Chertow GM, Fan D, et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*. 2004;351:1296–1305.
3. Levin A, Foley RN. Cardiovascular disease in chronic renal insufficiency. *Am J Kidney Dis*. 2000;36:S24–S30.
4. Drueke TB, Massy ZA. Atherosclerosis in CKD: differences from the general population. *Nat Rev Nephrol*. 2010;6:723–735.
5. Lindner A, Charra B, Sherrard DJ, Sribner BH. Accelerated atherosclerosis in prolonged maintenance hemodialysis. *N Engl J Med*. 1974;290:697–701.
6. Mall G, Rambausek M, Neumeister A, et al. Myocardial interstitial fibrosis in experimental uremia—implications for cardiac compliance. *Kidney Int*. 1988;33:804–811.
7. Amann K, Breitbach M, Ritz E, Mall G. Myocyte/capillary mismatch in the heart of uremic patients. *J Am Soc Nephrol*. 1998;9:1018–1022.
8. Blacher J, Safar ME, Guerin AP, et al. Aortic pulse wave velocity index and mortality in end-stage renal disease. *Kidney Int*. 2003;63:1852–1860.
9. Guerin AP, Blacher J, Pannier B, et al. Impact of aortic stiffness attenuation on survival of patients in end-stage renal failure. *Circulation*. 2001;103:987–992.
10. Foley RN, Parfrey PS, Morgan J, et al. Effect of hemoglobin levels in hemodialysis patients with asymptomatic cardiomyopathy. *Kidney Int*. 2000;58:1325–1335.

11. Ikram H, Lynn KL, Bailey RR, Little PJ. Cardiovascular changes in chronic hemodialysis patients. *Kidney Int*. 1983;24:371–376.
12. Levin A, Thompson CR, Ethier J, et al. Left ventricular mass index increase in early renal disease: impact of decline in hemoglobin. *Am J Kidney Dis*. 1999;34:125–134.
13. London GM, Zins B, Pannier B, et al. Vascular changes in hemodialysis patients in response to recombinant human erythropoietin. *Kidney Int*. 1989;36:878–882.
14. Bazeley J, Wish JB. The evolution of target hemoglobin levels in anemia of chronic kidney disease. *Adv Chronic Kidney Dis*. 2019;26:229–236.
15. Chertow GM, Burke SK, Raggi P, et al. Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. *Kidney Int*. 2002;62:245–252.
16. Schlieper G, Schurgers L, Brandenburg V, et al. Vascular calcification in chronic kidney disease: an update. *Nephrol Dial Transplant*. 2016;31:31–39.
17. Drueke TB, Rostand SG. Progression of vascular calcification in uraemic patients: can it be stopped? *Nephrol Dial Transplant*. 2002;17:1365–1368.
18. Schantl AE, Verhulst A, Neven E, et al. Inhibition of vascular calcification by inositol phosphates derivatized with ethylene glycol oligomers. *Nat Commun*. 2020;11:721.
19. Qunibi W, Moustafa M, Muenz LR, et al. A 1-year randomized trial of calcium acetate versus sevelamer on progression of coronary artery calcification in hemodialysis patients with comparable lipid control: the Calcium Acetate Renagel Evaluation-2 (CARE-2) study. *Am J Kidney Dis*. 2008;51:952–965.
20. Floege J. Calcium-containing phosphate binders in dialysis patients with cardiovascular calcifications: should we CARE-2 avoid them? *Nephrol Dial Transplant*. 2008;23:3050–3052.