Arterial Stiffness in the Heart Disease of CKD

Luca Zanoli,[1] Paolo Lentini,[2] Marie Briet,[3] Pietro Castellino,[4] Andrew A. House,[5] Gerard M. London,[6] Lorenzo Malatino,[4] Peter A. McCullough,[7] Dimitri P. Mikhailidis,[8] and Pierre Boutouyrie[6,9,10]

[1]Sections of Nephrology and [4]Internal Medicine, Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy; [2]Division of Nephrology and Dialysis, St. Bassiano Hospital, Bassano del Grappa, Italy; [3]Institut National de la Santé et de la Recherche Médicale U1083, National Center for Scientific Research Joint Research Unit 6214, Centre Hospitalo-Universitaire d'Angers, Université d'Angers, Angers, France; [5]Department of Medicine, University of Western Ontario, London, Ontario, Canada; [6]Institut National de la Santé et de la Recherche Médicale U970, Paris, France; [7]Department of Medicine, Baylor University Medical Center, Baylor Heart and Vascular Institute, Baylor Jack and Jane Hamilton Heart and Vascular Hospital, Dallas, Texas; [8]Department of Clinical Biochemistry, University College London, London, UK; [9]Faculté de Médecine, Université Paris Descartes, Sorbonne Paris Cité, Paris, France; and [10]Department of Pharmacology, Hôpital Européen Georges-Pompidou, Assistance Publique–Hôpitaux de Paris, Paris, France

ABSTRACT

CKD frequently leads to chronic cardiac dysfunction. This complex relationship has been termed as cardiorenal syndrome type 4 or cardio-renal link. Despite numerous studies and reviews focused on the pathophysiology and therapy of this syndrome, the role of arterial stiffness has been frequently overlooked. In this regard, several pathogenic factors, including uremic toxins (*i.e.*, uric acid, phosphates, endothelin-1, advanced glycation end-products, and asymmetric dimethylarginine), can be involved. Their effect on the arterial wall, direct or mediated by chronic inflammation and oxidative stress, results in arterial stiffening and decreased vascular compliance. The increase in aortic stiffness results in increased cardiac workload and reduced coronary artery perfusion pressure that, in turn, may lead to microvascular cardiac ischemia. Conversely, reduced arterial stiffness has been associated with increased survival. Several approaches can be considered to reduce vascular stiffness and improve vascular function in patients with CKD. This review primarily discusses current understanding of the mechanisms concerning uremic toxins, arterial stiffening, and impaired cardiac function, and the therapeutic options to reduce arterial stiffness in patients with CKD.

JASN 30: 918–928, 2019. doi: https://doi.org/10.1681/ASN.2019020117

The link between CKD and cardiovascular (CV) events is well recognized.[1–3] CV risk increases in a graded fashion with progressive decrease in kidney function and reaches a zenith in ESRD, but can be reduced by renal transplantation. It is widely accepted that only part of this excessive CV risk is explained by traditional risk factors. The relationship between CKD and chronic cardiac dysfunction is complex and has been named cardiorenal syndrome type 4 or cardio-renal link.[1,2]

Arterial stiffness is a vascular biomarker[4] that is increased in patients with CKD,[5–8] even in those with a mildly impaired renal function,[5] and is associated with an independent increase in CV risk.[7,8] Conversely, at least in patients with advanced CKD, the reduction in aortic stiffness is associated with an improved survival independent of BP changes.[7] The increase of arterial stiffness in CKD is mostly caused by reduced renal excretion of vascular toxins, maladaptive metabolic and hormonal processes, and as a result, premature vascular aging. Also, in ESRD, RRT (dialysis) plays a role in the stiffening process and its consequences. Several therapeutic options have been proposed to reduce arterial stiffness, but most of them have been tested primarily in other settings (*i.e.*, hypertension and diabetes).

Herein, we review the role of arterial stiffening as an independent mediator of myocardial dysfunction in CKD and the strategies to reduce arterial stiffness and, possibly, CV risk.

FROM CKD TO VASCULAR RISK

The Role of Chronic Inflammation

Several mechanisms are involved in determining arterial stiffening in patients with CKD (Figure 1). Most of them

Published online ahead of print. Publication date available at www.jasn.org.

Correspondence: Dr. Luca Zanoli, Nephrology, Department of Clinical and Experimental Medicine, Policlinico Universitario, University of Catania, Via Santa Sofia 78, 95123 Catania, Italy. Email: zanoli.rastelli@gmail.com

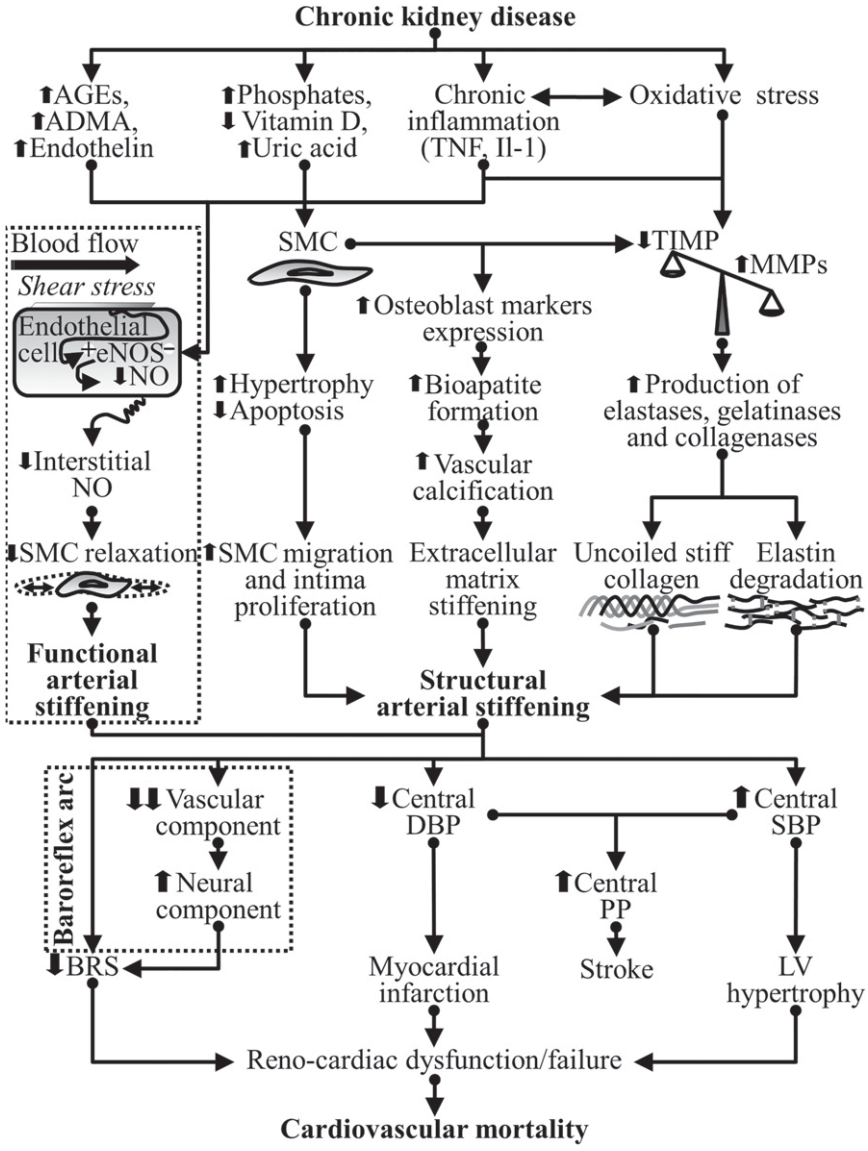

Figure 1. The vascular pathway in CKD. AGEs, advanced glycation end-products; BRS, baroreflex sensitivity; DBP, diastolic BP; LV, left ventricular; MMPs, matrix metalloproteinases; PP, pulse pressure; SBP, systolic BP; SMC, smooth muscle cell; TIMP, tissue inhibitor of matrix metalloproteinases. Modified from reference 14, with permission.

are shared with other physiologic (*i.e.*, age-related changes) and pathologic conditions (*i.e.*, chronic inflammatory disorders, hypertension, and diabetes). Patients with CKD have elevated levels of proinflammatory cytokines, such as TNF[9] and IL-6.[10] In patients with ESRD, chronic inflammation can be detected. In this context, dialysis can stimulate the immune system and lead to chronic inflammation. Moreover, short fragments of bacterial DNA, endotoxins, and small muramyl dipeptides can potentially be found in the dialysate and, after crossing through high-flux membranes, can induce the production of IL-6. Furthermore, the catheters used for either hemodialysis or peritoneal dialysis, as well as synthetic grafts, are potential sources of inflammation. In peritoneal dialysis, the high glucose content and glucose degradation products in conventional dialysis solutions can lead to the formation of advanced glycation end-products, oxidative stress, and chronic inflammation.[11]

Chronic inflammation can lead to arterial stiffening through several mechanisms. Increased levels of TNF can interfere with the activity of endothelial nitric oxide synthase (eNOS) and induce the production of reactive oxidative species.[12] Moreover, nitric oxide (NO) deficiency may itself cause oxidative stress.[13] Oxidative stress can lead to endothelial dysfunction through the reduction of the endothelial production of NO, and to structural arterial stiffening through the phenotypic switching of vascular smooth muscle cells (VSMCs), the production of matrix metalloproteinases, and the inhibition of the tissue inhibitors of matrix metalloproteinases.[14] In addition, TNF activates LDL receptor gene transcription, increases alkaline phosphatase protein expression, and reduces α-smooth muscle actin protein expression.[15] All of these processes, together with the infiltration of white blood cells into blood vessels and the direct toxic action of several uremic toxins (such as inorganic phosphate, advanced glycation end-products, and indoxyl sulfate [IS]), lead to the proliferation and changes in phenotype of VSMCs and the consequent release of matrix metalloproteinases, elastin fragmentation, collagen degradation, vascular calcification, and structural arterial stiffening.[15–17] The effect of TNF on the arterial wall is partially mediated by the release of IL-6 from VSMCs and endothelial cells. In other models of chronic severe inflammation (*i.e.*, inflammatory bowel disease and rheumatoid arthritis), chronic inflammation is associated with increased arterial stiffness and early return of reflected waves.[18–20] In these individuals, the inflammation-dependent aortic stiffening is at least in part reversible by anti-TNF therapy.[21,22] Despite these promising results in other models of chronic inflammation, baseline low-grade inflammation did not predict changes in arterial stiffness over time in CKD,[23] suggesting that, in parallel with chronic inflammation, other pathways can be involved in arterial stiffening in CKD. In this regard, the progressive accumulation of uremic toxins during CKD can also lead to arterial stiffening

via a direct toxicity on the arterial wall (see above).

Uremic Toxins Are Also Vascular Toxins

Under normal conditions, several calcification inhibitors, including pyrophosphate, adenosine, matrix Gla protein, osteopontin, fetuin-A, osteoprotegerin, and bone morphogenetic protein-7, protect against abnormal mineral deposition in the vessel wall, whereas hypercalcemia, increased levels of parathyroid hormone, inflammatory cytokines, oxidative stress, uremic toxins, advanced glycation end-products, and, most importantly, phosphates induce vascular calcification. During CKD there is an imbalance between inhibitors and inducers of vascular calcification.[24] Phosphates increase during CKD because of progressively reduced renal excretion. High phosphate levels may directly induce vascular calcification *via* the activation of Toll-like receptor 4/NF-κ light-chain enhancer of activated B cells (NF-κB) signaling in VSMCs.[25] Moreover, in the presence of high phosphate levels, VSMCs can change their phenotype into osteoblast-like cells *via* the loss of smooth muscle markers (*e.g.*, α-smooth muscle actin, SM22) and the expression of bone-forming genes (*e.g.*, core-binding factor α-1 Runx2/Cbfa1, Osterix, and alkaline phosphatase).[26] Phosphates could also directly modify mitochondrial function with high production of reactive oxygen species in parallel with activation of proinflammatory molecules and upregulation of TNF. These processes lead to vascular calcification and structural arterial stiffening. In this regard, calcium-phosphate mineral deposits are found in the subintimal and medial layer and represent the predominant vascular calcification in patients on dialysis. During CKD, several hormones that regulate serum phosphate levels by modulating intestinal phosphate absorption, renal phosphate reabsorption, and bone metabolism (*i.e.*, vitamin D, fetuin, klotho, and fibroblast growth factor 23), can have a role in arterial stiffening. These hormones can affect the arterial wall by the increase of phosphates levels and/or the development of vascular inflammation, endothelial dysfunction, and proliferation of VSMCs.

Another vascular toxin increased in patients with CKD is uric acid. This molecule attenuates NO production by decreasing the activity of the eNOS,[27] leads to the proliferation of VSMCs,[28] increases the expression of cyclooxygenase 2, stimulates the production of angiotensin II, and increases angiotensin-1 receptor expression in cultured VSMCs. Taken together, these effects suggest that uric acid may contribute to arterial stiffening in CKD.

Advanced glycation end-products are partially responsible for uremic vasculopathy. Advanced glycation end-products can progressively accumulate during CKD even in the absence of diabetes, as a consequence of reduced renal clearance and increased production. Advanced glycation end-products affect the phosphorylation status and expression of eNOS,[29] leading to endothelial dysfunction and functional arterial stiffening, and cause crosslinking of collagen molecules[30] and changes of the VSMCs phenotype,[17] leading to structural arterial stiffening. Moreover, as already mentioned for phosphates, advanced glycation end-products also activate NF-κB, which contributes to the development of vascular inflammation.

Asymmetric dimethylarginine (ADMA), an endogenous eNOS inhibitor, is another vascular toxin in CKD linked to arterial stiffening. Elevated levels of ADMA are reported during CKD likely related to reduced renal excretion and increased production caused by dysfunction of the endothelial L-arginine/NO pathway. ADMA is related to inflammation[31] and associated with left ventricular hypertrophy,[32] high sympathetic activity,[33] and increased CV risk.[31,33,34] ADMA can cause endothelial dysfunction through eNOS inhibition, and vascular remodeling through the amplification of oxidative stress. The inhibition of the NO production is enhanced in presence of eNOS polymorphisms.[35] Current data suggest that the blood flow in the forearm is reduced after the infusion of ADMA,[36] whereas systemic vascular resistance,[37] intima-media thickness,[38] and augmentation index are increased.[39]

Endothelin-1, a peptide with powerful vascular properties, increases during CKD, probably because of increased production and reduced clearance. The increased synthesis and release of endothelin-1 during CKD is regulated by angiotensin II, vasopressin, IL-1, oxidized LDL, cyclosporine, and a reduced extracellular pH.[40] Two receptor subtypes, ET_A and ET_B, with opposing actions, mediate the actions of endothelin.[40] ET_A receptors promote endothelial dysfunction, vascular inflammation, and vascular calcification *via* the induction of VSMCs differentiation into osteoblast-like cells, whereas ET_B receptors contribute to vasodilation, sodium excretion, and inhibition of inflammation.[40]

Cholesterol metabolism is altered in patients with CKD. Elevated triglycerides levels, frequently detected in patients with CKD, can lead to vascular inflammation, oxidative stress, oxidized LDL, foam cell production, VSMC proliferation, and endothelial dysfunction.[41] Recent evidence suggests that HDLs, frequently reduced in patients with CKD, may lose their CV protective properties and promote endothelial dysfunction and an abnormal vascular phenotype in patients with CKD.[42,43]

Recent experimental studies suggested that protein-bound uremic toxins, especially IS and p-cresyl sulfate, also contribute to the arterial phenotype observed in CKD. Acute *in vitro* exposure to IS increases VSMCs proliferation through a mechanism involving reactive oxygen species production and activation of mitogen-activated protein kinase P44/44 and P38, and aryl hydrocarbon receptor/NF-κB signaling pathways. In addition, IS has been shown to increase VSMC migration and senescence. p-Cresyl sulfate has pro-oxidative properties, but its effect on VSMC proliferation is still debated.[17]

The Arterial Phenotype of Patients with CKD

Several alterations of the arterial wall have been reported during CKD

(Figure 2).[5–7,44,45] Endothelial dysfunction can be detected starting from the early stages of CKD,[36] and can cause functional arterial stiffening,[46] whereas the structural alterations of the arterial wall, such as lipid deposition and atherosclerosis, result in an increased intima-media thickness and atherosclerotic plaque.[47] Changes of the intrinsic characteristics of the biomaterial, including vascular calcification, are evident from moderate CKD and are associated with structural changes and arterial stiffening.[5,14] In more advanced CKD, an enlargement of the carotid artery wall and outward remodeling are also reported.[6]

Interestingly, arterial remodeling during CKD seems to be different in elastic arteries (*i.e.*, aorta and carotid artery) and muscular arteries (*i.e.*, brachial, femoral, and renal artery), because aortic and carotid stiffness increases in patients with CKD whereas brachial and femoral stiffness does not increase and can be even reduced during CKD.[48,49] Loss of elastic fibers in the wall of the aorta has been reported in forms of aortic disease and can account for the circumstance of having aortic dilation yet reduced compliance in the same patient.[50] Finally, an inward remodeling (reduction of diameter) of the renal arteries has been reported in patients with CKD with a low prevalence of renal artery stenosis and a high CV risk.[51,52] The inward remodeling was associated with an increased risk of CV events.[53]

From Vascular Impairment to Cardiac Dysfunction

A well functioning arterial system is essential to receive pulsatile blood from the left ventricle and distribute it as a steady flow through the peripheral capillaries. Physiologically, during systole, approximately 50% of the stroke volume is momentarily stored within the aorta because of the elastic deformation of the arterial wall (cushioning function), whereas the remaining 50% is directly forwarded into the peripheral tissues (conduit function). During diastole, despite the blood flow from the left ventricle to the aorta being interrupted, a continuous blood flow from the aorta to the periphery is ensured by the discharge of the energy stored in the aortic wall. In individuals with elastic arteries, the forward wave originated by the contraction of the left ventricle propagates slowly from the aorta to the periphery; accordingly, the backward wave, originated by the reflection of the forward wave into the bifurcations and into the progressive reductions in the diameters of the arterial tree, propagates slowly from the periphery to the aorta. As a result of the slow propagation of the waves within the arterial tree, the backward wave meets the forward wave during diastole, thus contributing to the maintenance of a diastolic BP that is sufficient for tissue perfusion (Figure 3).

In the presence of increased arterial stiffness, the cushioning function of the aorta is altered and a larger part of the stroke volume is directly forwarded into the peripheral tissues during systole. Moreover, because the forward and backward waves propagate faster within the arterial tree, the reflected wave will meet the forward wave earlier (during systole), at the level of the aortic notch. The hemodynamic consequences of increased arterial stiffness and early return of reflected waves (*i.e.*, in patients with CKD) are a rise in central systolic BP, a drop in diastolic BP, and an increase in pulse pressure (Figure 1). The increased central systolic BP leads in turn to an augmented left ventricular work, oxygen requirement, and left ventricular hypertrophy; the decreased central diastolic BP is responsible for the decreased coronary artery perfusion pressure observed during diastole, with a consequent increased risk of myocardial ischemia; and the increased central pulse pressure leads to an increased risk of stroke. Because elastic arteries are specifically altered in CKD, and not muscular arteries, the physiologic gradient of stiffness (from low to high) is reversed in CKD.[54] The consequences of the reduced stiffness gradient is more transmission of pulsatility to the microcirculation.[55] In this regard, increased aortic stiffness is associated with white matter hyperintensity and lower cognitive function,[56] as well as CKD progression,[8] for the penetration of the energy of the pulse wave into low-resistance tissues like brain and kidneys. Therefore, increased arterial stiffness not only mediates at least some of the effects of CKD on cardiac function, but also affects the worsening of cardiorenal syndrome type 4.

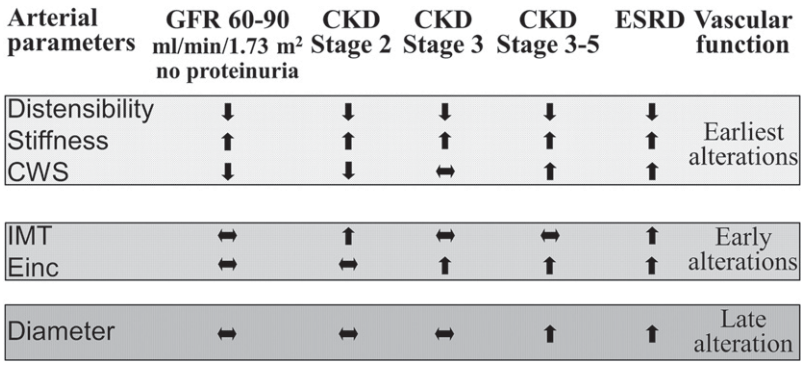

Figure 2. Carotid lesions in patients with CKD. CWS, circumferential wall stress; Einc, Young elastic modulus; IMT, intima-media thickness. Modified from reference 5, with permission.

Arterial Stiffening and Baroreflex Dysfunction

Arterial stiffening and baroreflex dysfunction, two conditions associated with an increased CV risk, seem to be strictly linked. Interestingly, both of them are detectable during CKD and are reverted after renal transplantation.[57,58] Given that baroreceptors are located in the carotid bulb and are sensitive to deformations of the arterial

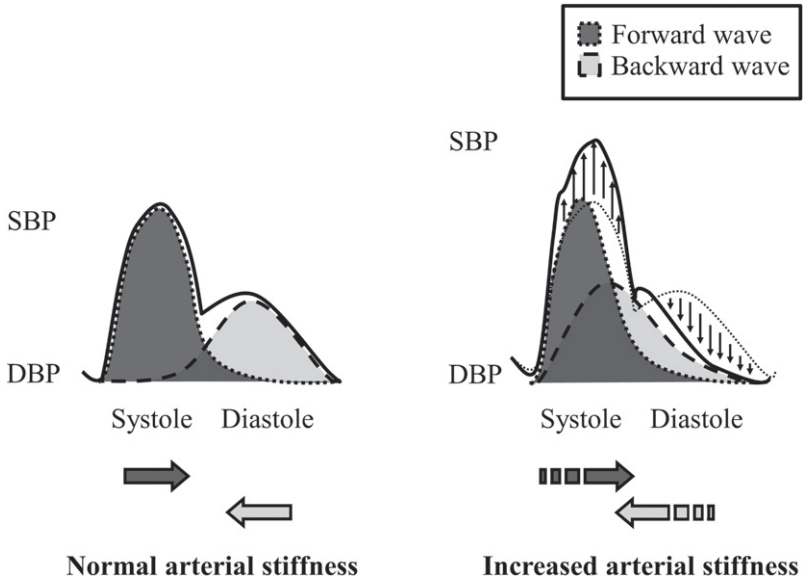

Figure 3. Arterial stiffness and pulse-wave propagation. DBP, diastolic BP; SBP, systolic BP. Modified from reference 14, with permission.

wall, two components of the baroreflex arc can be identified: the vascular component (which is arterial stiffness–dependent) and the neural component.[59] Baroreflex function can be impaired in individuals with increased arterial stiffness as consequence of the alteration of the vascular component.[60] Interestingly, in the presence of a stiff artery, the neural component of the baroreflex arc can also be hyperfunctioning to tentatively compensate for the reduced stimulation of the baroreceptors.[59] However, this counterregulation phenomenon is limited and cannot fully compensate for the increase in stiffness. In this case, the baroreflex function can be impaired when the hyperfunction of the neural component is not sufficient in counterbalancing the reduced stimulation of the baroreceptors.[59] It is possible, but not yet demonstrated, that the compensatory hyperfunction of the neural component is active at the early stages of CKD, in which an increased arterial stiffness is detectable and uremic toxins may not have affected the neural component. Further studies are needed to confirm this hypothesis and to evaluate the potential clinical consequences. On the other hand, sympathetic tone is raised in patients with CKD, particularly in the presence of ESRD.[61] In these patients, plasma norepinephrine correlates with concentric hypertrophy of the left ventricle and predicts survival in this clinical setting.[61,62] Moreover, high sympathetic overactivity and alterations in NO synthesis attributable to accumulation of the endogenous NO synthase inhibitor ADMA have been identified as potential causal mechanisms for the high CV mortality rates among patients with ESRD.[33] Finally, the sympathetic hyperactivity could be also considered a maladaptive mechanism to respond to the reduced stimulation of the baroreceptors, and an important part of a vicious circle: peripheral sympathetic hyperactivity leading to increased arterial stiffness,[63] leading to baroreflex dysfunction,[60] leading to peripheral sympathetic hyperactivity.

THERAPEUTIC OPTIONS TO REDUCE ARTERIAL STIFFNESS

The therapeutic options available to reduce arterial stiffness are reported in Table 1.

Antihypertensive Drugs

Arterial stiffness can be passively reduced by all antihypertensive drugs through a BP-dependent mechanism involving reduced stretching of the arterial wall. Few classes of antihypertensive drugs, such as angiotensin-converting enzyme inhibitors,[64] angiotensin receptor blockers, and direct renin inhibitors,[65] could reduce arterial stiffness even independently from BP changes, whereas β-blockers seem to be inferior to other classes of antihypertensive drugs in reducing central BP[66] and arterial stiffness.[67] In this regard, a profibrotic effect of celiprolol, a β1-andrenoceptor antagonist with partial β2 agonist activity, on the arterial wall has been recently reported in patients with Ehlers–Danlos syndrome.[68] In patients with ESRD, the insensitivity of aortic stiffness to decreased BP is an independent predictor of mortality, and the use of angiotensin-converting enzyme inhibitors has a favorable effect on survival that is independent of BP changes.[7] At least two classes of diuretics could have a beneficial effect on the arterial wall. Spironolactone reduces vascular and soft tissue calcification in Klotho-hypomorphic mice.[69] In this regard, aldosterone is associated with high levels of inactive matrix Gla protein, a vitamin K–dependent protein that inhibits arterial calcification.[70] Spironolactone could also reduce aortic stiffness in stage 3 CKD through the reduction of vascular fibrosis.[71] However, its use in more advanced stages of CKD should be carefully evaluated because of the risk of hyperkalaemia.[72] Sodium-glucose cotransporter-2 inhibitors, a new class of oral hypoglycemic/diuretic for the treatment of diabetes, have shown additional diuretic properties that could be potentially helpful in the early stages of CKD.[73] Moreover, sodium-glucose cotransporter-2 inhibitors can have a beneficial effect on the arterial wall through the reduction of circulatory levels of oxidants TNF and IL-6.[74] Their use in more advanced CKD is questionable.

Destiffening Strategies

Advanced glycation end-product breakers can improve endothelial function in several populations, including patients

Table 1. Qualitative summary of the available evidence on the effect of drugs used in nephrology on arterial wall properties

Drug(s)	Effect on Arterial Wall Properties	Best Level of Evidence	Level of Evidence in CKD or Kidney Transplant Recipients
AGEs breakers	↑ EF	+	+
Antihypertensive drugs			
ACEi	↓ AS	+++	++
ARBs	↓ AS	+++	++
DRi	↓ AS	++	+
β-blockers	Doubtful		
Calcium channel blockers	↓ AS	+++	+
Diuretics (spironolactone)	↓ AS	+	+
Antioxidants			
Ascorbic acid	↓ AS	++	++
Endothelin-1 antagonists	↓ AS, ↑ EF	+	+
Immunosuppressive drugs			
Anti-TNF	↓ AS	+++	°
Cyclosporine	↑ AS	++	++
Tacrolimus	Doubtful		
Everolimus or sirolimus	Doubtful		
Belatacept	Doubtful		
Mycophenolate mofetil	↓ AS	+	+
Corticosteroids	↑ AS	+	°
Salicylates (low doses)	↓ AS	++	°
Salicylates (high doses)	↑ AS	+	°
Lipid-lowering drugs			
Statins	↑ EF	+	+
Noncalcium-containing phosphate binders	↓ AS	+	+
Parathyroid hormone	Doubtful		
Xanthine oxidase inhibitors			
Allopurinol	↑ EF	+++	+
Vitamin D analogs			
Vitamin D_2	None	+++	++
Vitamin D_3	None	+++	++
Paricalcitol	↑ EF	+++	++

Arrows indicate increase or decrease. AGEs, advanced glycation end-products; EF, endothelial function; +, data derived from few single-center cohorts; ACEi, angiotensin-converting enzyme inhibitors; AS, arterial stiffness; +++, evidence on the basis of meta-analysis; ++, large number of evidence derived from multiple single-center cohorts; ARBs, angiotensin II receptor blockers; DRi, direct renin inhibitors; °, lack of or scarce data.

with CKD.[75] Moreover, the use of alagebrium, an advanced glycation end-product breaker, is inversely correlated with plasma matrix metalloproteinase-9 and type 1 collagen,[75] suggesting that this drug could also reduce the structural arterial stiffness. However, phase 2 trials have reported no changes in BP and aortic distensibility in the alagebrium group.[76] Therefore, more clinical trials are necessary to further evaluate the potential beneficial effect of advanced glycation end-product breakers in patients with CKD.

Anti-inflammatory drugs reduce chronic inflammation, which has a favorable effect on arterial stiffness in several populations. Only the most recent targeted drugs have proven efficacy. In other models of chronic inflammation and increased arterial stiffness, it has been reported that the long-term use of anti-TNF therapy can revert aortic stiffening to a level comparable with matched controls,[21,22] whereas a high dose of salicylic acid had the opposite effect.[77] In patients with CKD, although reducing chronic inflammation could be attempted with anti-inflammatory drugs and through the reduction of uremic toxins, the use of anti-inflammatory drugs cannot be recommended because of their detrimental effects on renal function[78] and the lack of data on the effect of anti-inflammatory drugs on arterial stiffness in these patients. Promising results on endothelial function and CV events has been recently reported in patients treated with anti–IL-1 inhibitors.[79] Antioxidant drugs are good candidates for destiffening arteries. The administration of ascorbic acid, a potent antioxidant, can be attempted to improve flow-mediated dilation and reduce central BP and ADMA in patients with CKD.[80,81]

There is evidence that endothelin receptor antagonists reduce arterial stiffness in nondiabetic patients with CKD.[82] Whether this reduction is independent of BP remains unknown. Magnesium is a natural calcium antagonist with a vasodilator effect. It increases the production of NO, alters the vascular response to endothelin-1, angiotensin II, and catecholamines and inhibits the

proliferation of VSMCs. Magnesium levels rise during advanced CKD and ESRD because of the progressive reduction of renal excretion.[83] However, several drugs currently used in patients with CKD, such as proton pump inhibitors, loop diuretics, and cyclosporine, can lead to hypomagnesaemia.[84] The risk of hypomagnesaemia increases when these drugs are used in combination. Magnesium supplementation and the shift from proton pump inhibitors to H_2 antagonists is sufficient to restore magnesium levels in most patients with CKD. Long-term magnesium supplementation improves arterial stiffness in overweight and obese adults, whereas increasing dialysate magnesium decreases the propensity toward ectopic calcification in patients undergoing maintenance hemodialysis.[85,86] Also, zinc may play a similar role in the arterial wall.[87]

It has been reported that decreasing gastrointestinal phosphate absorption through the use of phosphate binders not containing calcium (*i.e.*, sevelamer hydrochloride) reduces arterial stiffness in patients with ESRD.[88] However, similar results have not been replicated in early stages of CKD.[89] It is plausible that a long follow-up period (possibly years) is needed to revert the structural arterial stiffening caused by vascular calcification.

Statins prevent the development of endothelial dysfunction caused by acute inflammation in patients with hypercholesterolemia,[90] and slow the rate of an increase in aortic stiffness in patients with CKD.[91] They may also exert beneficial effects on kidney function and slow down the rate of decline in kidney function.[92,93] Interestingly, the protective effect of statins on CV events seems to be reduced in patients undergoing hemodialysis,[94] and improved by the coadministration of ezetimibe.[95]

Vitamin D is a regulator of eNOS and arterial stiffness. The effect of vitamin D analog supplementation on vascular function has been evaluated in three meta-analyses that also included a minority of patients with CKD.[96–98] In two meta-analyses, vitamin D analog supplementation was associated with improved endothelial function.[97,98] In the third meta-analysis,[96] paricalcitol, but not vitamin D_2 or vitamin D_3, improved endothelial function. However, a high vitamin D level carries the risk of aggravating hyperphosphatemia, which could again be detrimental to endothelial function. All three meta-analyses were concordant regarding the lack of an effect on arterial stiffness and reflected waves.[96–98]

There is evidence of a protective effect of allopurinol, a drug that reduces plasma uric acid levels, on endothelial function in patients with and without CKD.[99] Allopurinol administration significantly reduced augmentation index, but not arterial stiffness.[100]

Specific Therapeutic Options to Reduce Arterial Stiffness in ESRD

Several immunosuppressive drugs that are currently used in kidney transplant recipients may influence arterial function. Everolimus and sirolimus, two mammalian target of rapamycin inhibitors, could have beneficial effects on atherogenesis and fibrosis.[101,102] However, whether these drugs are useful in reducing arterial stiffness is still matter of debate because arterial stiffness was reduced or remained stable in patients treated with sirolimus, and increased in those treated with cyclosporine, a calcineurin inhibitor.[103] Conversely, in a cross-sectional study, endothelial dysfunction was more frequent in patients treated with everolimus plus a calcineurin inhibitor, compared with those treated with mycophenolate mofetil plus a calcineurin inhibitor.[104] The immunosuppressant biotherapy belatacept inhibits costimulatory signals that are essential for T lymphocyte activation *via* the binding to CD80 and CD86 receptors on antigen-presenting cells. This drug could reduce vascular inflammation through the inhibition of the production of proinflammatory cytokines by activated T lymphocytes, as suggested by the reduction of antihypertensive medications at 1 year in patients treated with belatacept compared with those treated with cyclosporine.[105] However, the results of two small, cross-sectional studies have not confirmed this hypothesis.[106,107] Therefore, further longitudinal studies are needed to better clarify the effect of belatacept on the arterial wall. Immunosuppressive drugs may also have a negative effect on the arterial wall. In particular, cyclosporine reduces NO production, leads to vasoconstriction and vascular fibrosis, and accelerates the stiffening process.[108] In this regard, the switch to tacrolimus could potentially help to improve arterial stiffness. However, this hypothesis is still matter of debate. Finally, corticosteroids have a deleterious effect on the arterial wall, at least in part through the increase of BP (through salt retention and hyperactivation of the renin-angiotensin-aldosterone system) and LDL cholesterol levels.[109]

Renal transplantation is an effective approach to reduce arterial stiffness in patients with ESRD.[58] The improvement in arterial stiffness is better if kidneys come from young donors (living as opposed to deceased).[110] Similar to the reduction of arterial stiffness, the baroreflex sensitivity is also improved after a renal transplant.[57] However, the mechanism by which renal transplantation can improve baroreflex function, as well as the relationship between baroreflex function and arterial properties, needs to be clarified.[111]

Dialysis modalities can influence the alteration in arterial stiffness. Arterial stiffness can be reduced through the use of convective dialysis techniques (such as a high-efficiency, on-line hemodiafiltration), rather than conventional hemodialysis, for the increased removal of middle molecular weight uremic toxins (*i.e.*, β2-microglobulin, phosphate, and TNF) and protein kinase Cβ2, which is an eNOS inhibitor.[112] The use of convective dialysis techniques also reduce chronic inflammation and mortality risk compared with conventional hemodialysis.[113,114]

PERSPECTIVES

Reducing arterial stiffness can be attempted by several approaches, but few of them

have been tested in patients with CKD. Moreover, we are far away from confirming that the treatment options discussed in this review independently reduce CV events or delay the progression of CKD. At the time of this review, only one trial has demonstrated that patients who improve their arterial stiffness during intervention have better outcomes.[7] Therefore, large-scale, randomized trials that include long-term measures of vascular stiffness and recording cardiac and renal events are needed in patients with CKD.

In conclusion, vascular dysfunction is an important mediator between CKD and chronic impairment of cardiac function. Several therapeutic approaches can be attempted to reduce arterial stiffness in patients with CKD.

ACKNOWLEDGMENTS

This study was partially funded by the 2016/2018 Department Research Plan of University of Catania, Department of Clinical and Experimental Medicine (project #A).

DISCLOSURES

None.

REFERENCES

1. Granata A, Clementi A, Virzì GM, Brocca A, de Cal M, Scarfia VR, et al: Cardiorenal syndrome type 4: From chronic kidney disease to cardiovascular impairment. *Eur J Intern Med* 30: 1–6, 2016
2. Zoccali C, Goldsmith D, Agarwal R, Blankestijn PJ, Fliser D, Wiecek A, et al.: The complexity of the cardio-renal link: Taxonomy, syndromes, and diseases. *Kidney Int Suppl* (2011) 1: 2–5, 2011
3. Capodanno D, Marcantoni C, Ministeri M, Dipasqua F, Zanoli L, Rastelli S, et al: Incorporating glomerular filtration rate or creatinine clearance by the modification of diet in renal disease equation or the Cockcroft-Gault equations to improve the global accuracy of the Age, Creatinine, Ejection Fraction [ACEF] score in patients undergoing percutaneous coronary intervention. *Int J Cardiol* 168: 396–402, 2013
4. Vlachopoulos C, Xaplanteris P, Aboyans V, Brodmann M, Cífková R, Cosentino F, et al: The role of vascular biomarkers for primary and secondary prevention. A position paper from the European Society of Cardiology Working Group on peripheral circulation: Endorsed by the Association for Research into Arterial Structure and Physiology (ARTERY) Society. *Atherosclerosis* 241: 507–532, 2015
5. Zanoli L, Empana JP, Perier MC, Alivon M, Ketthab H, Castellino P, et al: Increased carotid stiffness and remodelling at early stages of chronic kidney disease. [published online ahead of print January 7, 2019] *J Hypertens* doi: 10.1097/HJH.0000000000002007
6. Briet M, Bozec E, Laurent S, Fassot C, London GM, Jacquot C, et al: Arterial stiffness and enlargement in mild-to-moderate chronic kidney disease. *Kidney Int* 69: 350–357, 2006
7. Guerin AP, Blacher J, Pannier B, Marchais SJ, Safar ME, London GM: Impact of aortic stiffness attenuation on survival of patients in end-stage renal failure. *Circulation* 103: 987–992, 2001
8. Townsend RR: Arterial stiffness in CKD: A review. *Am J Kidney Dis* 73: 240–247, 2019
9. Wallquist C, Mansouri L, Norrbäck M, Hylander B, Jacobson SH, Lundahl J: Early changes in monocyte adhesion molecule expression and tumor necrosis factor-α levels in chronic kidney disease - a 5-year prospective study. *Am J Nephrol* 44: 268–275, 2016
10. Desjardins MP, Sidibé A, Fortier C, MacWay F, Marquis K, De Serres S, et al.: Association of interleukin-6 with aortic stiffness in end-stage renal disease. *J Am Soc Hypertens* 12: 5–13, 2018
11. Miyata T, Horie K, Ueda Y, Fujita Y, Izuhara Y, Hirano H, et al.: Advanced glycation and lipidoxidation of the peritoneal membrane: Respective roles of serum and peritoneal fluid reactive carbonyl compounds. *Kidney Int* 58: 425–435, 2000
12. Kataoka H, Murakami R, Numaguchi Y, Okumura K, Murohara T: Angiotensin II type 1 receptor blockers prevent tumor necrosis factor-alpha-mediated endothelial nitric oxide synthase reduction and superoxide production in human umbilical vein endothelial cells. *Eur J Pharmacol* 636: 36–41, 2010
13. Sárközy M, Kovács ZZA, Kovács MG, Gáspár R, Szűcs G, Dux L: Mechanisms and modulation of oxidative/nitrative stress in type 4 cardio-renal syndrome and renal sarcopenia. *Front Physiol* 9: 1648, 2018
14. Zanoli L, Rastelli S, Inserra G, Castellino P: Arterial structure and function in inflammatory bowel disease. *World J Gastroenterol* 21: 11304–11311, 2015
15. Liu J, Ma KL, Gao M, Wang CX, Ni J, Zhang Y, et al.: Inflammation disrupts the LDL receptor pathway and accelerates the progression of vascular calcification in ESRD patients. *PLoS One* 7: e47217, 2012
16. Zieman SJ, Melenovsky V, Kass DA: Mechanisms, pathophysiology, and therapy of arterial stiffness. *Arterioscler Thromb Vasc Biol* 25: 932–943, 2005
17. Hénaut L, Mary A, Chillon JM, Kamel S, Massy ZA: The impact of uremic toxins on vascular smooth muscle cell function. *Toxins (Basel)* 10: 218, 2018
18. Zanoli L, Boutouyrie P, Fatuzzo P, Granata A, Lentini P, Oztürk K, et al.: Inflammation and aortic stiffness: An individual participant data meta-analysis in patients with inflammatory bowel disease. *J Am Heart Assoc* 6: e007003, 2017
19. Zanoli L, Granata A, Lentini P, Gaudio A, Castellino P: Augmentation index is increased in patients with inflammatory bowel disease, a meta-analysis. *Eur J Intern Med* 39: e31–e32, 2017
20. Ambrosino P, Tasso M, Lupoli R, Di Minno A, Baldassarre D, Tremoli E, et al.: Noninvasive assessment of arterial stiffness in patients with rheumatoid arthritis: A systematic review and meta-analysis of literature studies. *Ann Med* 47: 457–467, 2015
21. Zanoli L, Ozturk K, Cappello M, Inserra G, Geraci G, Tuttolomondo A, et al.: Inflammation and aortic pulse wave velocity: A multicenter longitudinal study in patients with inflammatory bowel disease. *J Am Heart Assoc* 8: e010942, 2019
22. Vlachopoulos C, Gravos A, Georgiopoulos G, Terentes-Printzios D, Ioakeimidis N, Vassilopoulos D, et al.: The effect of TNF-a antagonists on aortic stiffness and wave reflections: A meta-analysis. *Clin Rheumatol* 37: 515–526, 2018
23. Peyster E, Chen J, Feldman HI, Go AS, Gupta J, Mitra N, et al.; CRIC Study Investigators: Inflammation and arterial stiffness in chronic kidney disease: Findings from the CRIC study. *Am J Hypertens* 30: 400–408, 2017
24. Vervloet M, Cozzolino M: Vascular calcification in chronic kidney disease: Different bricks in the wall? *Kidney Int* 91: 808–817, 2017
25. Zhang D, Bi X, Liu Y, Huang Y, Xiong J, Xu X, et al.: High phosphate-induced calcification of vascular smooth muscle cells is associated with the TLR4/NF-κb signaling pathway. *Kidney Blood Press Res* 42: 1205–1215, 2017
26. Lacolley P, Regnault V, Segers P, Laurent S: Vascular smooth muscle cells and arterial stiffening: Relevance in development, aging, and disease. *Physiol Rev* 97: 1555–1617, 2017
27. Park JH, Jin YM, Hwang S, Cho DH, Kang DH, Jo I: Uric acid attenuates nitric oxide production by decreasing the interaction between endothelial nitric oxide synthase and calmodulin in human umbilical vein endothelial cells: A mechanism for uric acid-induced cardiovascular disease

development. *Nitric Oxide* 32: 36–42, 2013
28. Mazzali M, Kanellis J, Han L, Feng L, Xia YY, Chen Q, et al.: Hyperuricemia induces a primary renal arteriolopathy in rats by a blood pressure-independent mechanism. *Am J Physiol Renal Physiol* 282: F991–F997, 2002
29. Jamwal S, Sharma S: Vascular endothelium dysfunction: A conservative target in metabolic disorders. *Inflamm Res* 67: 391–405, 2018
30. Aronson D: Cross-linking of glycated collagen in the pathogenesis of arterial and myocardial stiffening of aging and diabetes. *J Hypertens* 21: 3–12, 2003
31. Tripepi G, Mattace Raso F, Sijbrands E, Seck MS, Maas R, Boger R, et al.: Inflammation and asymmetric dimethylarginine for predicting death and cardiovascular events in ESRD patients. *Clin J Am Soc Nephrol* 6: 1714–1721, 2011
32. Zoccali C, Mallamaci F, Maas R, Benedetto FA, Tripepi G, Malatino LS, et al.; CREED Investigators: Left ventricular hypertrophy, cardiac remodeling and asymmetric dimethylarginine (ADMA) in hemodialysis patients. *Kidney Int* 62: 339–345, 2002
33. Mallamaci F, Tripepi G, Maas R, Malatino L, Böger R, Zoccali C: Analysis of the relationship between norepinephrine and asymmetric dimethyl arginine levels among patients with end-stage renal disease. *J Am Soc Nephrol* 15: 435–441, 2004
34. Zoccali C, Bode-Böger S, Mallamaci F, Benedetto F, Tripepi G, Malatino L, et al.: Plasma concentration of asymmetrical dimethylarginine and mortality in patients with end-stage renal disease: A prospective study. *Lancet* 358: 2113–2117, 2001
35. Testa A, Spoto B, Tripepi G, Mallamaci F, Malatino L, Fatuzzo P, et al.: The GLU298ASP variant of nitric oxide synthase interacts with asymmetric dimethyl arginine in determining cardiovascular mortality in patients with end-stage renal disease. *J Hypertens* 23: 1825–1830, 2005
36. Calver A, Collier J, Leone A, Moncada S, Vallance P: Effect of local intra-arterial asymmetric dimethylarginine (ADMA) on the forearm arteriolar bed of healthy volunteers. *J Hum Hypertens* 7: 193–194, 1993
37. Achan V, Broadhead M, Malaki M, Whitley G, Leiper J, MacAllister R, et al.: Asymmetric dimethylarginine causes hypertension and cardiac dysfunction in humans and is actively metabolized by dimethylarginine dimethylaminohydrolase. *Arterioscler Thromb Vasc Biol* 23: 1455–1459, 2003
38. Zoccali C, Benedetto FA, Maas R, Mallamaci F, Tripepi G, Malatino LS, et al.; CREED Investigators: Asymmetric dimethylarginine, C-reactive protein, and carotid intima-media thickness in end-stage renal disease. *J Am Soc Nephrol* 13: 490–496, 2002
39. Kielstein JT, Donnerstag F, Gasper S, Menne J, Kielstein A, Martens-Lobenhoffer J, et al.: ADMA increases arterial stiffness and decreases cerebral blood flow in humans. *Stroke* 37: 2024–2029, 2006
40. Dhaun N, Goddard J, Webb DJ: The endothelin system and its antagonism in chronic kidney disease. *J Am Soc Nephrol* 17: 943–955, 2006
41. Reiss AB, Voloshyna I, De Leon J, Miyawaki N, Mattana J: Cholesterol Metabolism in CKD. *Am J Kidney Dis* 66: 1071–1082, 2015
42. Shroff R, Speer T, Colin S, Charakida M, Zewinger S, Staels B, et al.: HDL in children with CKD promotes endothelial dysfunction and an abnormal vascular phenotype. *J Am Soc Nephrol* 25: 2658–2668, 2014
43. Zewinger S, Speer T, Kleber ME, Scharnagl H, Woitas R, Lepper PM, et al: HDL cholesterol is not associated with lower mortality in patients with kidney dysfunction. *J Am Soc Nephrol* 25: 1073–1082, 2014
44. London GM, Pannier B, Marchais SJ: Vascular calcifications, arterial aging and arterial remodeling in ESRD. *Blood Purif* 35: 16–21, 2013
45. Stam F, van Guldener C, Becker A, Dekker JM, Heine RJ, Bouter LM, et al: Endothelial dysfunction contributes to renal function-associated cardiovascular mortality in a population with mild renal insufficiency: The Hoorn study. *J Am Soc Nephrol* 17: 537–545, 2006
46. Wilkinson IB, Qasem A, McEniery CM, Webb DJ, Avolio AP, Cockcroft JR: Nitric oxide regulates local arterial distensibility in vivo. *Circulation* 105: 213–217, 2002
47. McCullough PA, Chinnaiyan KM, Agrawal V, Danielewicz E, Abela GS: Amplification of atherosclerotic calcification and Mönckeberg's sclerosis: A spectrum of the same disease process. *Adv Chronic Kidney Dis* 15: 396–412, 2008
48. Zanoli L, Lentini P, Boutouyrie P, Fatuzzo P, Granata A, Corrao S, et al: Pulse wave velocity differs between ulcerative colitis and chronic kidney disease. *Eur J Intern Med* 47: 36–42, 2018
49. Kim ED, Tanaka H, Ballew SH, Sang Y, Heiss G, Coresh J, et al: Associations between kidney disease measures and regional pulse wave velocity in a large community-based cohort: The Atherosclerosis Risk in Communities (ARIC) study. *Am J Kidney Dis* 72: 682–690, 2018
50. Roberts WC, McCullough SP, Vasudevan A: Characteristics of adults having aortic valve replacement for pure aortic regurgitation involving a congenitally bicuspid aortic valve unaffected by infective endocarditis or aortic dissection. *Am J Cardiol* 122: 2104–2111, 2018
51. Marcantoni C, Rastelli S, Zanoli L, Tripepi G, Di Salvo M, Monaco S, et al: Prevalence of renal artery stenosis in patients undergoing cardiac catheterization. *Intern Emerg Med* 8: 401–408, 2013
52. Zanoli L, Rastelli S, Marcantoni C, Tamburino C, Laurent S, Boutouyrie P, et al: Renal artery diameter, renal function and resistant hypertension in patients with low-to-moderate renal artery stenosis. *J Hypertens* 30: 600–607, 2012
53. Zanoli L, Rastelli S, Marcantoni C, Capodanno D, Blanco J, Tamburino C, et al: Non-hemodynamically significant renal artery stenosis predicts cardiovascular events in persons with ischemic heart disease. *Am J Nephrol* 40: 468–477, 2014
54. Fortier C, Mac-Way F, Desmeules S, Marquis K, De Serres SA, Lebel M, et al: Aortic-brachial stiffness mismatch and mortality in dialysis population. *Hypertension* 65: 378–384, 2015
55. Fortier C, Agharazii M: Arterial stiffness gradient. *Pulse (Basel)* 3: 159–166, 2016
56. Singer J, Trollor JN, Baune BT, Sachdev PS, Smith E: Arterial stiffness, the brain and cognition: A systematic review. *Ageing Res Rev* 15: 16–27, 2014
57. Kaur M, Chandran DS, Jaryal AK, Bhowmik D, Agarwal SK, Deepak KK: Baroreflex dysfunction in chronic kidney disease. *World J Nephrol* 5: 53–65, 2016
58. Sidibé A, Fortier C, Desjardins MP, Zomahoun HTV, Boutin A, Mac-Way F, et al.: Reduction of arterial stiffness after kidney transplantation: A systematic review and meta-analysis. *J Am Heart Assoc* 6: e007235, 2017
59. Zanoli L, Empana JP, Estrugo N, Escriou G, Ketthab H, Pruny JF, et al: The neural baroreflex pathway in subjects with metabolic syndrome: A sub-study of the paris prospective study III. *Medicine (Baltimore)* 95: e2472, 2016
60. Mattace-Raso FU, van den Meiracker AH, Bos WJ, van der Cammen TJ, Westerhof BE, Elias-Smale S, et al.: Arterial stiffness, cardiovagal baroreflex sensitivity and postural blood pressure changes in older adults: The Rotterdam Study. *J Hypertens* 25: 1421–1426, 2007
61. Zoccali C, Mallamaci F, Parlongo S, Cutrupi S, Benedetto FA, Tripepi G, et al.: Plasma norepinephrine predicts survival and incident cardiovascular events in patients with end-stage renal disease. *Circulation* 105: 1354–1359, 2002
62. Zoccali C, Mallamaci F, Tripepi G, Parlongo S, Cutrupi S, Benedetto FA, et al.; CREED Investigators: Norepinephrine and concentric hypertrophy in patients with end-stage renal disease. *Hypertension* 40: 41–46, 2002
63. Nardone M, Incognito AV, Millar PJ: Evidence for pressure-independent sympathetic modulation of central pulse wave velocity. *J Am Heart Assoc* 7: e007971, 2018
64. Shahin Y, Khan JA, Chetter I: Angiotensin converting enzyme inhibitors effect on arterial stiffness and wave reflections: A meta-analysis and meta-regression of

randomised controlled trials. *Atherosclerosis* 221: 18–33, 2012
65. Raptis AE, Markakis KP, Mazioti MC, Ikonomidis I, Maratou EP, Vlahakos DV, et al.: Effect of aliskiren on circulating endothelial progenitor cells and vascular function in patients with type 2 diabetes and essential hypertension. *Am J Hypertens* 28: 22–29, 2015
66. McGaughey TJ, Fletcher EA, Shah SA: Impact of antihypertensive agents on central systolic blood pressure and augmentation index: A meta-analysis. *Am J Hypertens* 29: 448–457, 2016
67. Niu W, Qi Y: A meta-analysis of randomized controlled trials assessing the impact of beta-blockers on arterial stiffness, peripheral blood pressure and heart rate. *Int J Cardiol* 218: 109–117, 2016
68. Ong KT, Perdu J, De Backer J, Bozec E, Collignon P, Emmerich J, et al.: Effect of celiprolol on prevention of cardiovascular events in vascular Ehlers-Danlos syndrome: A prospective randomised, open, blinded-endpoints trial. *Lancet* 376: 1476–1484, 2010
69. Voelkl J, Alesutan I, Leibrock CB, Quintanilla-Martinez L, Kuhn V, Feger M, et al: Spironolactone ameliorates PIT1-dependent vascular osteoinduction in klotho-hypomorphic mice. *J Clin Invest* 123: 812–822, 2013
70. Chirinos JA, Sardana M, Syed AA, Koppula MR, Varakantam S, Vasim I, et al.: Aldosterone, inactive matrix glaprotein, and large artery stiffness in hypertension. *J Am Soc Hypertens* 12: 681–689, 2018
71. Edwards NC, Steeds RP, Stewart PM, Ferro CJ, Townend JN: Effect of spironolactone on left ventricular mass and aortic stiffness in early-stage chronic kidney disease: A randomized controlled trial. *J Am Coll Cardiol* 54: 505–512, 2009
72. Georgianos PI, Vaios V, Eleftheriadis T, Zebekakis P, Liakopoulos V: Mineralocorticoid antagonists in ESRD: An overview of clinical trial evidence. *Curr Vasc Pharmacol* 15: 599–606, 2017
73. Zanoli L, Granata A, Lentini P, Rastelli S, Fatuzzo P, Rapisarda F, et al.: Sodium-glucose linked transporter-2 inhibitors in chronic kidney disease. *ScientificWorldJournal* 2015: 317507, 2015
74. Tahara A, Kurosaki E, Yokono M, Yamajuku D, Kihara R, Hayashizaki Y, et al.: Effects of SGLT2 selective inhibitor ipragliflozin on hyperglycemia, hyperlipidemia, hepatic steatosis, oxidative stress, inflammation, and obesity in type 2 diabetic mice. *Eur J Pharmacol* 715: 246–255, 2013
75. Zieman SJ, Melenovsky V, Clattenburg L, Corretti MC, Capriotti A, Gerstenblith G, et al.: Advanced glycation endproduct crosslink breaker (alagebrium) improves endothelial function in patients with isolated systolic hypertension. *J Hypertens* 25: 577–583, 2007
76. Borg DJ, Forbes JM: Targeting advanced glycation with pharmaceutical agents: Where are we now? *Glycoconj J* 33: 653–670, 2016
77. Zanoli L, Boutouyrie P, Lentini P, Rastelli S, Castellino P: Maintenance therapy with salicylates is associated with aortic stiffening in patients with inflammatory bowel disease. *J Hypertens* 35: 898–899, 2017
78. Zhang X, Donnan PT, Bell S, Guthrie B: Non-steroidal anti-inflammatory drug induced acute kidney injury in the community dwelling general population and people with chronic kidney disease: Systematic review and meta-analysis. *BMC Nephrol* 18: 256, 2017
79. Nowak KL, Chonchol M, Ikizler TA, Farmer-Bailey H, Salas N, Chaudhry R, et al.: IL-1 inhibition and vascular function in CKD. *J Am Soc Nephrol* 28: 971–980, 2017
80. Ghiadoni L, Cupisti A, Huang Y, Mattei P, Cardinal H, Favilla S, et al.: Endothelial dysfunction and oxidative stress in chronic renal failure. *J Nephrol* 17: 512–519, 2004
81. Gillis K, Stevens KK, Bell E, Patel RK, Jardine AG, Morris STW, et al: Ascorbic acid lowers central blood pressure and asymmetric dimethylarginine in chronic kidney disease. *Clin Kidney J* 11: 532–539, 2018
82. Dhaun N, MacIntyre IM, Kerr D, Melville V, Johnston NR, Haughie S, et al.: Selective endothelin-A receptor antagonism reduces proteinuria, blood pressure, and arterial stiffness in chronic proteinuric kidney disease. *Hypertension* 57: 772–779, 2011
83. van de Wal-Visscher ER, Kooman JP, van der Sande FM: Magnesium in chronic kidney disease: Should we care? *Blood Purif* 45: 173–178, 2018
84. Zanoli L, Lentini P, Fatuzzo P: Digoxin and hypermagnesuria. *Nephron* 138: 89–91, 2018
85. Joris PJ, Plat J, Bakker SJ, Mensink RP: Long-term magnesium supplementation improves arterial stiffness in overweight and obese adults: Results of a randomized, double-blind, placebo-controlled intervention trial. *Am J Clin Nutr* 103: 1260–1266, 2016
86. Bressendorff I, Hansen D, Schou M, Pasch A, Brandi L: The effect of increasing dialysate magnesium on serum calcification propensity in subjects with end stage kidney disease: A randomized, controlled clinical trial. *Clin J Am Soc Nephrol* 13: 1373–1380, 2018
87. Voelkl J, Tuffaha R, Luong TTD, Zickler D, Masyout J, Feger M, et al.: Zinc inhibits phosphate-induced vascular calcification through TNFAIP3-mediated suppression of NF-κB. *J Am Soc Nephrol* 29: 1636–1648, 2018
88. Iimori S, Mori Y, Akita W, Takada S, Kuyama T, Ohnishi T, et al.: Effects of sevelamer hydrochloride on mortality, lipid abnormality and arterial stiffness in hemodialyzed patients: A propensity-matched observational study. *Clin Exp Nephrol* 16: 930–937, 2012
89. Chue CD, Townend JN, Moody WE, Zehnder D, Wall NA, Harper L, et al.: Cardiovascular effects of sevelamer in stage 3 CKD. *J Am Soc Nephrol* 24: 842–852, 2013
90. Vlachopoulos C, Aznaouridis K, Dagre A, Vasiliadou C, Masoura C, Stefanadi E, et al.: Protective effect of atorvastatin on acute systemic inflammation-induced endothelial dysfunction in hypercholesterolaemic subjects. *Eur Heart J* 28: 2102–2109, 2007
91. Fassett RG, Robertson IK, Ball MJ, Geraghty DP, Sharman JE, Coombes JS: Effects of atorvastatin on arterial stiffness in chronic kidney disease: A randomised controlled trial. *J Atheroscler Thromb* 17: 235–241, 2010
92. Athyros VG, Katsiki N, Karagiannis A, Mikhailidis DP: Statins can improve proteinuria and glomerular filtration rate loss in chronic kidney disease patients, further reducing cardiovascular risk. Fact or fiction? *Expert Opin Pharmacother* 16: 1449–1461, 2015
93. Sanguankeo A, Upala S, Cheungpasitporn W, Ungprasert P, Knight EL: Effects of statins on renal outcome in chronic kidney disease patients: A systematic review and meta-analysis. *PLoS One* 10: e0132970, 2015
94. Fellström BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, et al: Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *N Engl J Med* 360: 1395–1407, 2009
95. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, et al.; SHARP Investigators: The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): A randomised placebo-controlled trial. *Lancet* 377: 2181–2192, 2011
96. Beveridge LA, Khan F, Struthers AD, Armitage J, Barchetta I, Bressendorff I, et al.: Effect of vitamin D supplementation on markers of vascular function: A systematic review and individual participant meta-analysis. *J Am Heart Assoc* 7: e008273, 2018
97. Mazidi M, Karimi E, Rezaie P, Vatanparast H: The impact of vitamin D supplement intake on vascular endothelial function; a systematic review and meta-analysis of randomized controlled trials. *Food Nutr Res* 61: 1273574, 2017
98. Tabrizi R, Vakili S, Lankarani KB, Akbari M, Jamilian M, Mahdizadeh Z, et al.: The effects of vitamin D supplementation on markers related to endothelial function among patients with metabolic syndrome and related disorders: A systematic review

and meta-analysis of clinical trials. *Horm Metab Res* 50: 587–596, 2018
99. Xin W, Mi S, Lin Z: Allopurinol therapy improves vascular endothelial function in subjects at risk for cardiovascular diseases: A meta-analysis of randomized controlled trials. *Cardiovasc Ther* 34: 441–449, 2016
100. Deng G, Qiu Z, Li D, Fang Y, Zhang S: Effects of allopurinol on arterial stiffness: A meta-analysis of randomized controlled trials. *Med Sci Monit* 22: 1389–1397, 2016
101. Martinet W, De Loof H, De Meyer GRY: mTOR inhibition: A promising strategy for stabilization of atherosclerotic plaques. *Atherosclerosis* 233: 601–607, 2014
102. Haller ST, Yan Y, Drummond CA, Xie J, Tian J, Kennedy DJ, et al.: Rapamycin attenuates cardiac fibrosis in experimental uremic cardiomyopathy by reducing marinobufagenin levels and inhibiting downstream profibrotic signaling. *J Am Heart Assoc* 5: e004106, 2016
103. Seckinger J, Sommerer C, Hinkel UP, Hoffmann O, Zeier M, Schwenger V: Switch of immunosuppression from cyclosporine A to everolimus: Impact on pulse wave velocity in stable de-novo renal allograft recipients. *J Hypertens* 26: 2213–2219, 2008
104. Ruben S, Kreuzer M, Büscher A, Büscher R, Thumfart J, Querfeld U, et al.: Impaired microcirculation in children after kidney transplantation: Everolimus versus mycophenolate based immunosuppression regimen. *Kidney Blood Press Res* 43: 793–806, 2018
105. Masson P, Henderson L, Chapman JR, Craig JC, Webster AC: Belatacept for kidney transplant recipients. *Cochrane Database Syst Rev* 11: CD010699, 2014
106. Seibert FS, Steltzer J, Melilli E, Grannas G, Pagonas N, Bauer F, et al.: Differential impact of belatacept and cyclosporine A on central aortic blood pressure and arterial stiffness after renal transplantation. *Clin Transplant* 28: 1004–1009, 2014
107. Melilli E, Bestard-Matamoros O, Manonelles-Montero A, Sala-Bassa N, Mast R, Grinyó-Boira JM, et al.: Arterial stiffness in kidney transplantation: A single center case-control study comparing belatacept versus calcineurin inhibitor immunosuppressive based regimen. *Nefrologia* 35: 58–65, 2015
108. Roullet JB, Xue H, McCarron DA, Holcomb S, Bennett WM: Vascular mechanisms of cyclosporin-induced hypertension in the rat. *J Clin Invest* 93: 2244–2250, 1994
109. Sholter DE, Armstrong PW: Adverse effects of corticosteroids on the cardiovascular system. *Can J Cardiol* 16: 505–511, 2000
110. Karras A, Boutouyrie P, Briet M, Bozec E, Haymann JP, Legendre C, et al.: Reversal of arterial stiffness and maladaptative arterial remodeling after kidney transplantation. *J Am Heart Assoc* 6: e006078, 2017
111. Boutouyrie P, Zanoli L, Briet M, Karras A, Delahousse M: Baroreflex sensitivity after kidney transplantation: Arterial or neural improvement? *Nephrol Dial Transplant* 28: 2401–2403, 2013
112. Bellien J, Fréguin-Bouilland C, Joannidès R, Hanoy M, Rémy-Jouet I, Monteil C, et al.: High-efficiency on-line haemodiafiltration improves conduit artery endothelial function compared with high-flux haemodialysis in end-stage renal disease patients. *Nephrol Dial Transplant* 29: 414–422, 2014
113. den Hoedt CH, Bots ML, Grooteman MP, van der Weerd NC, Mazairac AH, Penne EL, et al.; CONTRAST Investigators: Online hemodiafiltration reduces systemic inflammation compared to low-flux hemodialysis. *Kidney Int* 86: 423–432, 2014
114. Cernaro V, Tripepi G, Visconti L, Lacquaniti A, Montalto G, Romeo A, et al.; Workgroup of the Sicilian Registry of Nephrology, Dialysis and Transplantation: Convective dialysis reduces mortality risk: Results from a large observational, population-based analysis. *Ther Apher Dial* 22: 457–468, 2018