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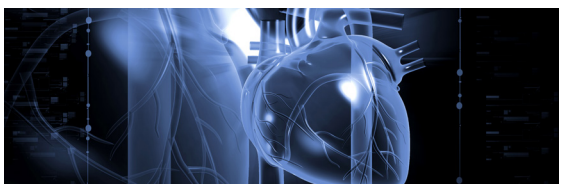
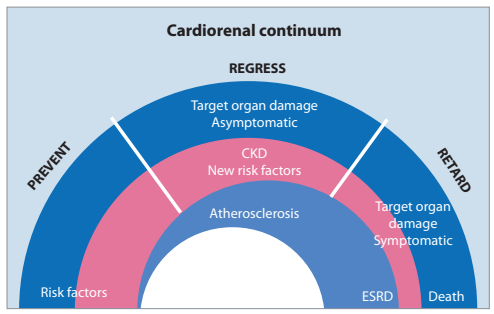


Core concepts



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Combined impact of chronic kidney disease and contrast-induced nephropathy on long-term outcomes in patients with ST-segment elevation acute myocardial infarction who undergo primary percutaneous coronary intervention

Contrast-induced nephropathy (CIN) and chronic kidney disease (CKD) are associated with poor outcomes after primary percutaneous coronary intervention (PCI) for acute myocardial infarction (AMI); however, its combined prognostic significance remains unclear. We enrolled 577 patients with AMI undergoing primary PCI within 12 h after symptom onset and measured serum creatinine on admission and the next 3 days. CKD was defined as admission estimated glomerular filtration rate < 60 ml/min/1.73 m^2, and CIN was defined as creatinine increase ≥0.5 mg/dl or ≥25 % from baseline within the first 72 h. Patients were stratified according to the presence or absence of CKD and CIN. In patients with no CKD and no CIN (n = 244), no CKD but CIN (n = 152), CKD but no CIN (n = 127), and both CKD and CIN (n = 54), the 3-year major adverse cardiovascular events (MACE: a combination of all-cause mortality, nonfatal reinfarction, or heart failure requiring rehospitalization) were 8, 9, 13, and 35 %, respectively (p < 0.001). Multivariate analysis showed that as compared with no CKD and no CIN, hazard ratios (95 % CI) for MACE associated with no CKD but CIN, CKD but no CIN, and both CKD and CIN were 0.91 (0.44–1.84; p = 0.79), 1.11 (0.5–2.23; p = 0.77), and 2.98 (1.48–6.04; p = 0.002), respectively. In patients with AMI undergoing primary PCI, the combination of CKD and CIN is significantly associated with adverse long-term outcomes.

References available on request
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Source: Hidefumi Nakahashi, Masami Kosuge, Kentaro Sakamaki, et al. Combined impact of chronic kidney di`sease and contrast-induced nephropathy on long-term outcomes in patients with ST-segment elevation acute myocardial infarction who undergo primary percutaneous coronary intervention. Heart Vessels 2017;32:22–29. DOI 10.1007/s00380-016-0836-8.

Impact of decreased serum albumin levels on acute kidney injury in patients with acute decompensated heart failure: a potential association of atrial natriuretic peptide

Although hypoalbuminemia at admission is a risk for acute kidney injury (AKI) and mortality in patients with acute decompensated heart failure (ADHF), the clinical significance of decreased serum albumin levels (DAL) during ADHF therapy has not been elucidated. This study aimed to evaluate whether DAL was associated with AKI, and whether intravenous atrial natriuretic peptide (ANP) administration, which provides an effective treatment for ADHF but promotes albumin extravasation, was associated with DAL and AKI. A total of 231 consecutive patients with ADHF were enrolled. AKI was defined as ≥0.3 mg/ dl absolute or 1.5-fold increase in serum creatinine levels within 48 h. AKI occurred in 73 (32 %) of the 231 patients during ADHF therapy. The median value of decreases in serum albumin levels was 0.3 g/dl at 7 days after admission. When DAL was defined as ≥0.3 g/dl decrease in serum albumin levels, DAL occurred in 113 patients, and was independently associated with AKI. Of the 231 patients, 73 (32 %) were treated with intravenous ANP. DAL occurred more frequently in patients receiving ANP than in those not receiving ANP (77 vs. 36 %, p < 0.001), and ANP was independently associated with DAL. The incidence of AKI was higher in patients receiving ANP than in those not receiving ANP (48 vs. 24 %, p < 0.001). ANP was independently associated with AKI. In conclusion, DAL is associated with AKI. Intravenous ANP administration may be one of the promoting factors of DAL, which leads to AKI, indicating a possible novel mechanism of AKI.

References available on request
Healthcare.India@springer.com

Source: Yoichi Takaya, Fumiki Yoshihara, Hiroyuki Yokoyama, et al. Impact of decreased serum albumin levels on acute kidney injury in patients with acute decompensated heart failure: a potential association of atrial natriuretic peptide. Heart Vessels 2017. Advance online publication. DOI 10.1007/s00380-017-0954-y.

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Hypertension and chronic kidney disease

Stephanie Riggen, Rajiv Agarwal

Treatment of hypertension in chronic kidney disease (CKD) patients is important to delay progression of renal function loss. Based on critical review of evidence, guidelines have been developed to assist in treating hypertension in patients with CKD. Renovascular hypertension and ischemic nephropathy as well as resistant hypertension are common complex diagnoses in patients with hypertension and kidney disease that require further investigation and treatment.

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Before You Start: Facts You Need to Know

- Hypertension is the second leading cause of ESRD in the United States.
- Uncontrolled hypertension is associated with accelerated progression to ESRD.
- Recent genetic advances may provide more information on the cause and effect relationship of hypertension and kidney disease.
- Renovascular hypertension and ischemic nephropathy are associated with progressive chronic kidney disease but their diagnosis and treatment remain complex and challenging.
- Treatment of hypertension in CKD patients is important to delay progression of renal function loss and to protect against cardiovascular disease.
- Resistant hypertension is defined as blood pressure that remains above goal (such as 140/90) in spite of the concurrent use of 3 antihypertensive agents of different classes.

Worldwide, hypertension is a major public health problem and is associated with morbidity and mortality due to cardiovascular and kidney diseases. In the United States, hypertension is present in approximately 80–85 % of patients with CKD and is the second leading cause of ESRD in the United States after diabetes. Uncontrolled hypertension is associated with accelerated progression to ESRD. This association was prospectively studied among 332,544 men screened for the Multiple Risk Factor Intervention Trial (MRFIT); among the 814 subjects who either died of or were treated for ESRD, it was found that elevated blood pressure was a strong independent risk factor for ESRD [1].

Although the association of hypertension and ESRD was strong, this study did not prove a cause and effect relationship. In fact, whether hypertension causes CKD or is a

result of CKD or both remains debated.

The diagnosis of hypertensive nephrosclerosis is a diagnosis of exclusion; it is a clinical diagnosis based on history, physical examination, urinalysis, and laboratory testing. The diagnosis is typically made in patients with chronic kidney disease who have had long-standing hypertension and subnephrotic range proteinuria without evidence of other kidney disease (based on serologic testing and imaging tests). Few patients diagnosed with hypertensive nephrosclerosis undergo renal biopsy.

Histologic lesions of hypertensive nephrosclerosis are characterized by changes in vascular, glomerular, and tubulointerstitial structures For example, vascular changes are characterized by afferent arteriolar narrowing and fibrosis, arteriosclerosis and arteriolosclerosis, and intimal fibrosis; glomerular changes by hyalinosis, global glomerulosclerosis, and segmental glomerulosclerosis; and tubulointerstitial changes by atrophy, inflammation, and fibrosis.

To examine the accuracy of the diagnosis of hypertensive nephrosclerosis, an examination of renal biopsies was performed on a subset of patients enrolled in the African American Study of Kidney Disease (AASK) Trial, a trial that was designed to examine the impact of antihypertensive therapies and two levels of blood pressure control on the rate of progression of renal dysfunction in African Americans with presumed hypertensive renal disease. The AASK pilot biopsy study of 39 patients showed 38 patients with arteriosclerosis and/or arteriolosclerosis [2]. This confirmed that renal biopsies in nondiabetic hypertensive African Americans with mild to moderate renal insufficiency in the absence of nephrotic proteinuria are likely to show changes consistent with what we call hypertensive nephrosclerosis as outlined above.

The mechanism by which hypertension causes renal dysfunction is based on animal models, which have demonstrated that autoregulation protects the glomerular microcirculation from high arterial pressures. In certain conditions, such as chronic kidney disease and diabetes, this autoregulation is impaired, which is associated with glomerular injury and glomerulosclerosis. Although some evidence from human studies support the concept of autoregulatory dysfunction at the level of the glomerular microcirculation, the evidence from animals are much stronger.

Just as hypertension may cause CKD, CKD may also cause hypertension. Why this may be so is multifactorial. These factors include sodium retention, increased activity of the renin-angiotensin system and sympathetic nervous system, and impaired nitric oxide synthesis and endothelium-mediated vasodilatation in uremic patients. Patients with CKD frequently have sleep apnea and secondary hyperparathyroidism, both of which can contribute to hypertension with the latter causing increased intracellular calcium concentration leading to vasoconstriction. Besides, the circadian variation in BP is profoundly disturbed. Ambulatory blood pressure monitoring in patients with CKD often identifies a loss of normal decline in blood pressure of 10 % during sleep, such patients are termed "nondippers," which has been associated with an increased risk of left ventricular hypertrophy and cardiovascular events [3]. The diagnosis of hypertensive nephrosclerosis has been called into question with the discovery of the association of specific genes with kidney disease. Molecular genetic advances, particularly mapping by admixture linkage disequilibrium (MALD) analyses, pointed to a cluster of polymorphisms in the *MYH9* gene on chromosome 22 that were strongly associated with African ancestry nondiabetic kidney disease. However, Genovese *et al.* searched an expanded risk interval and found a statistically stronger genetic association with kidney disease in *APOL1*, the gene encoding apolipoprotein L-1, which is located <20 kb from the 3' end of *MYH9* [4].

The two *APOL1* risk allele variants, G1 and G2, have been found to be strongly associated with nondiabetic kidney disease, particularly FSGS. It is hypothesized that patients with *APOL1* risk variant alleles have a genetic predisposition to kidney disease and then suffer a "second hit" such as a gene-gene or gene-environment interaction leading to various histologic forms of nondiabetic kidney disease and perhaps many patients who are labeled as having "hypertensive nephrosclerosis" actually have an underlying genetic predisposition to kidney disease [5].

The normal in vivo functions of *APOL1* and the mechanism of kidney injury are unknown. Interestingly, however, *APOL1* risk variants likely rose to high frequency in sub-Saharan Africa due to conferring protection from African sleeping sickness caused by trypanosomes. Genovese *et al.* found that serum from carriers of *APOL1* risk variants demonstrated a trypanolytic effect on *Trypanosoma brucei rhodesiense* and absence of trypanosomal killing with serum from individuals lacking *APOL1* risk variants [4]. Thus, the *APOL1* risk variants provided a likely selective advantage to carriers against African sleeping sickness, but unfortunately, possession of two *APOL1* risk variants is associated with increased risk of kidney disease. This story is similar to the protection of malaria by HgbS.

Just as hypertension may cause CKD, CKD may also cause hypertension. Why this may be so is multifactorial.

As more data emerges regarding genetic and environmental influences on the development of kidney disease, some have proposed that hypertensive kidney disease is a no longer useful term and a more generic term of arterionephrosclerosis should be used.

Renovascular hypertension and ischemic nephropathy

Renovascular disease is a term used to describe several clinical syndromes resulting from reduced perfusion to the kidney including ischemic renal disease and renovascular hypertension. Ischemic renal disease occurs when renal blood flow falls below the level of renal autoregulation and leads to reduced GFR and renal atrophy. On the other hand, renovascular hypertension (RVH) is defined as a syndrome of elevated blood pressure that is produced as a result of a variety of conditions that cause renal ischemia. The most common cause of RVH is main renal artery stenosis (RAS), either by fibromuscular dysplasia or atherosclerotic renal vascular disease.

Mechanisms responsible for sustained RVH differ according to whether one or both kidneys are affected by significant stenosis. Both situations have impaired renal perfusion, which activates the renin-angiotensin system causing sodium retention. However, when there is still one functioning kidney (in experimental animals this is simulated by one clipped renal artery, with two kidneys present and is termed "two-kidney hypertension"), pressure natriuresis can occur in the functioning kidney eliminating excess sodium. This leads to a sustained decreased perfusion to the stenotic

side, leading to sustained activation of the renin-angiotensin system. Hypertension in this situation is angiotensin II-dependent hypertension with secondary aldosterone excess. On the other hand when the vascular lesion involves both kidneys or affects a solitary functioning kidney (termed "one-kidney hypertension"), there is no normal kidney to counteract the increased systemic pressure. Sodium is thus retained and blood volume expanded, which feeds back to inhibit the renin-angiotensin system. However, the renin-angiotensin system activation is inappropriately activated for the degree of sodium retention.

Renovascular disease can have varied presentations. Clinical features that may alert to the presence of renovascular disease include an acute rise of serum creatinine of at least 30 % after administration of ACE inhibitor or ARB (often accompanied by hypotension), a unilateral small kidney, or asymmetry in renal size of more than 1.5 cm that cannot be explained by another reason, moderate to severe hypertension in patients with recurrent episodes of flash pulmonary edema, late onset of severe hypertension (after age of 55 years), or presence of an abdominal bruit.

The diagnosis of RVH requires demonstration of a critical stenotic vascular lesion affecting the renal artery. Luminal occlusion of less than 60 % rarely reduces either pressure or blood flow. RVH usually only occurs when luminal occlusion is relatively severe, usually in the 70–80 % occlusion range.

American College of Cardiology/ American Heart Association (ACC/AHA) developed guidelines to assist clinicians with the diagnosis, medical treatment, and revascularization for renal artery stenosis (Box 1).

The gold standard for diagnosing renal artery stenosis is renal arteriography but is usually performed only after a less invasive

Box 1. What the guidelines say you should do: renal artery stenosis (RAS) [6].

Clinical Clues to Diagnosis

Class I Recommendations

- The performance of diagnostic studies to identify clinically significant RAS is indicated in patients with the onset of hypertension before the age of 30 years
- The performance of diagnostic studies to identify clinically significant RAS is indicated in patients with the onset of severe hypertension [as defined in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC-7 report] after the age of 55 years
- The performance of diagnostic studies to identify clinically significant RAS is indicated in patients with the following characteristics: (a) accelerated hypertension (sudden and persistent worsening of previously controlled hypertension), (b) resistant hypertension (defined as the failure to achieve goal blood pressure in patients who are adhering to full doses of an appropriate 3-drug regimen that includes a diuretic), or (c) malignant hypertension (hypertension with coexistent evidence of acute end-organ damage)
- The performance of diagnostic studies to identify clinically significant RAS is indicated in patients with new azotemia or worsening renal function after the administration of an ACE inhibitor or/and angiotensin receptor blocking agent
- The performance of diagnostic studies to identify clinically significant RAS is indicated in patients with sudden, unexplained pulmonary edema (especially in azotemic patients)

Class IIa Recommendations

- The performance of diagnostic studies to identify clinically significant RAS is reasonable in patients with unexplained renal failure, including individuals starting renal replacement therapy (dialysis or renal transplantation)
- Class IIb The performance of arteriography to identify significant RAS may be reasonable in patients with multivessel coronary artery disease and none of the clinical clues or PAD at the time of arteriography
- The performance of diagnostic studies to identify clinically significant RAS may be reasonable in patients with unexplained congestive heart failure or refractory angina

Diagnostic Methods for Renal Artery Stenosis

Class I

- Duplex ultrasonography is recommended as a screening test to establish the diagnosis of RAS
- Computed tomographic angiography (in individuals with normal renal function) is recommended as a screening test to establish the diagnosis of RAS
- Magnetic resonance angiography is recommended as a screening test to establish the diagnosis of RAS
- When the clinical index of suspicion is high and the results of the noninvasive tests are inconclusive, catheter angiography is recommended as a diagnostic test to establish the diagnosis of RAS

Class III

- Captopril renal scintigraphy is not recommended as a screening test to establish the diagnosis of RAS
- Selective renal vein renin measurements are not recommended as a useful screening test to establish the diagnosis of RAS
- Plasma renin activity is not recommended as a useful screening test to establish the diagnosis of RAS
- The captopril test (measurement of plasma renin activity after captopril administration) is not recommended as a useful screening test to establish the diagnosis of RAS

Medical Treatment for Renal Artery Stenosis

Class I

- Angiotensin-converting enzyme inhibitors are effective medications for treatment of hypertension associated with unilateral RAS Angiotensin receptor blockers are effective medications for treatment of hypertension associated with unilateral RAS
- Calcium-channel blockers are effective medications for the treatment of hypertension associated with unilateral RAS
- Beta-blockers are effective medications for treatment of hypertension associated with RAS

Indications for Revascularization for Renal Artery Stenosis

Asymptomatic Stenosis

Class IIb

- Percutaneous revascularization may be considered for treatment of an asymptomatic bilateral or solitary viable kidney with a hemodynamically significant RAS
- The usefulness of percutaneous revascularization of an asymptomatic unilateral hemodynamically significant RAS in a viable kidney is not well established and is presently clinically unproven

Hypertension

Class IIa

- Percutaneous revascularization is reasonable for patients with hemodynamically significant RAS and accelerated hypertension, resistant hypertension, malignant hypertension, hypertension with unexplained unilateral small kidney, and hypertension with intolerance to medication

Preservation of Renal Function

Class IIa

- Percutaneous revascularization is reasonable for patients with RAS and progressive chronic kidney disease with bilateral RAS or a RAS to a solitary functioning kidney

Class IIb

- Percutaneous revascularization may be considered for patients with RAS and chronic renal insufficiency with unilateral RAS

Congestive Heart Failure and Unstable Angina

Class I

- Percutaneous revascularization is indicated for patients with hemodynamically significant RAS and recurrent, unexplained congestive heart failure or sudden, unexplained pulmonary edema

Class IIa

- Percutaneous revascularization is reasonable for patients with hemodynamically significant RAS and unstable angina

test has increased the likelihood of an accurate diagnosis. Less invasive tests include duplex Doppler ultrasonography, CTA, or MRA. The test of choice should be based on institutional expertise and patient factors as radiocontrast and gadolinium are potentially harmful in patients with CKD stage 4 or 5. Captopril renal scintigraphy, selective renal vein renin measurements, and plasma renin activity are not useful as initial diagnostic tests for renal artery stenosis.

It has been suggested that calculation of resistance index by duplex Doppler ultrasonography can identify patients who are likely or not to respond to revascularization. A high resistive index was associated with a poor outcome and may indicate irreversible intrarenal vascular disease.

Once diagnosed, the optimal treatment for the patient is not clear. Patients with atherosclerotic renovascular disease have a high rate of systemic atherosclerosis and are at increased risk for adverse cardiovascular outcomes. The increased cardiovascular risk in patients with atherosclerotic renal artery stenosis may be due to mechanisms activated by the renal artery stenosis or due to the high likelihood that these patients have atherosclerosis in multiple vascular beds. Treatment should address modifiable cardiovascular risk factors, including weight loss, smoking cessation, treatment of hyperlipidemia, and blood pressure and glucose control.

There are no definitive randomized controlled trial data to guide clinicians on specific antihypertensive medical therapies in patients with RAS. It would appear that the first-line therapy should be directed at the principal mechanism thought to be responsible for the elevated blood pressure, activation of the renin-angiotensin-aldosterone system. Although blockade of the renin-angiotensin system is considered fundamental, it is contraindicated in most patients. Antihypertensive agents that block the renin-angiotensin system remove the vasoconstrictive action of angiotensin II (AII) at the efferent arteriole. When pre-glomerular pressures are reduced for any reason, blockade of AII causes the kidney to lose its compensatory ability to preserve glomerular transcapillary filtration pressures by constricting the efferent arteriole. This can lead to "functional acute renal insufficiency." Paying particular importance to volume status and cardiac function and monitoring serum creatinine if ever agents that block the renin-angiotensin system are initiated are important in limiting renal toxicity in these patients.

Whether to treat patients with medical therapy alone or with revascularization has been evaluated in several randomized clinical trials. These trials, including the ASTRAL trial, showed a lack of benefit of revascularization using BP as an endpoint. The ASTRAL trial was a multicenter, randomized, unblinded trial of 806 patients with atherosclerotic renovascular disease assigned to undergo either revascularization in addition to medical therapy or to medical therapy alone with a primary outcome of renal function. During a 5-year period, patients in the group who underwent revascularization had a slightly slower rate of progression of renal impairment; however, the change was too small to offer clinical benefit. In addition there was no significant difference in a secondary endpoint of systolic blood pressure between the two groups. The two groups had similar rates of renal events, major cardiovascular events, and death. Given serious complications associated with revascularization occurred in 23 patients including 2 deaths, the investigators concluded that there was an increased risk but no evidence of significant clinical benefit from revascularization in patients with atherosclerotic renovascular disease. The major limitation of the ASTRAL trial was that the population enrolled only included patients who their own physician was uncertain as to whether revascularization would provide a clinical benefit leaving an unresolved question of whether some patients with severe renal artery stenosis may benefit from revascularization [8].

The CORAL trial, cardiovascular outcomes in renal atherosclerotic lesions, is an ongoing trial that was designed to answer the question if stent revascularization of hemodynamically significant atherosclerotic RAS in hypertensive patients when added upon medical therapy can prevent adverse cardiovascular and renal events. It has been proposed that atherosclerotic renal artery stenosis has many other deleterious effects throughout the body other than causing elevated blood pressure and that treating RAS with revascularization may be beneficial in ways other than lowering blood pressure. The results of this trial may provide guidance for a disease whose diagnosis and treatment remain complex and challenging at present [9].

BP control in CKD

Treatment of hypertension in CKD patients is important to delay progression of renal function loss and to protect against cardiovascular disease. KDIGO clinical practice guidelines for management of blood pressure in chronic kidney disease are based on quality of evidence (Boxes 2 and 3).

BP goals should be individualized according to age, coexistent cardiovascular disease and other comorbidities, risk of progression of CKD, presence or absence of retinopathy (in CKD patients with diabetes), and tolerance of treatment. Evidence supports a goal blood pressure ≤140/90 mmHg for CKD patients without proteinuria defined as albuminuria <30 mg/24 h, regardless of diabetes status. Since proteinuria has been associated with worse kidney outcomes, stricter BP control is

Box 2. What the guidelines say you should do: management of blood pressure in non-dialysis-dependent CKD patients without diabetes mellitus [10].

- We recommend that nondiabetic adults with non-dialysis-dependent CKD and urine albumin excretion <30 mg per 24 h whose office BP is consistently >140 mmHg systolic or >90 mmHg diastolic be treated with BP-lowering agents to maintain a BP that is consistently ≤140 mmHg systolic and ≤90 mmHg diastolic (1B).
- We suggest that nondiabetic adults with non-dialysis-dependent CKD and urine albumin excretion of 30–300 mg per 24 h whose office BP is consistently >130 mmHg systolic or >80 mmHg diastolic be treated with BP-lowering agents to maintain a BP that is consistently ≤130 systolic and ≤80 mmHg diastolic (2D).
- We suggest that nondiabetic adults with non-dialysis-dependent CKD and urine albumin excretion >300 mg per 24 h whose office BP is consistently >130 mmHg systolic or >80 mmHg diastolic be treated with BP-lowering agents to maintain a BP that is consistently ≤130 systolic and ≤80 mmHg diastolic (2C).
- We suggest that an ARB or ACE-I be used in nondiabetic adults with nondialysis-dependent CKD and urine albumin excretion of 30–300 mg per 24 h in whom treatment with BP-lowering drugs is indicated (2D).
- We recommend that an ARB or ACE-I be used in nondiabetic adults with nondialysis- dependent CKD and urine albumin excretion >300 mg per 24 h in whom treatment with BP-lowering drugs is indicated (1B).

Box 3. What the guidelines say you should do: management of blood pressure in non-dialysis-dependent CKD patients with diabetes mellitus [10].

- We recommend that adults with diabetes and non-dialysis-dependent CKD and urine albumin excretion <30 mg per 24 h whose office BP is consistently >140 mmHg systolic or >90 mmHg diastolic be treated with BP-lowering agents to maintain a BP that is consistently ≤140 mmHg systolic and ≤90 mmHg diastolic [1B].
- We suggest that adults with diabetes and non-dialysis-dependent CKD urine albumin excretion of >30 mg per 24 h whose office BP is consistently >130 mmHg systolic or >80 mmHg diastolic be treated with BP-lowering agents to maintain a BP that is consistently ≤130 mmHg systolic and ≤80 mmHg diastolic [2D].
- We suggest that an ARB or ACE-I be used in adults with diabetes and nondialysis-dependent CKD with urine albumin excretion of 30–300 mg per 24 h [2D].
- We recommend that an ARB or ACE-I be used in adults with diabetes and non-dialysis-dependent CKD with urine albumin excretion >300 mg per 24 h [1B].

recommended with goal BP ≤130/80 mmHg in both diabetic and nondiabetic patients with albuminuria >30 mg/24 h.

A meta-analysis by Jafar *et al.* was performed to determine the levels of blood pressure and urine protein excretion associated with the lowest risk of progression of CKD using antihypertensive therapy with and without ACE inhibitors. Although the data must be interpreted with caution as the clinical trials were not designed to primarily assess this, the meta-analysis on 1860 nondiabetic patients from 11 randomized, controlled trials showed that systolic blood pressure of 110–129 mmHg and urine protein excretion of less than 2 g/day were associated with the lowest risk for kidney disease progression. The risk of progression increased with urine protein excretion greater than 1 g/day and systolic blood pressures greater than 120–130 mmHg. The results of the meta-analysis, which were consistent with the results of the MDRD and AASK trials, showed that lowering blood pressure is more beneficial in delaying progression of kidney disease in patients with higher levels of proteinuria [11].

Although BP control has been shown to delay progression of kidney disease, more aggressive blood pressure control has not been shown to be better. Three main randomized controlled trials, MDRD, AASK, and REIN2, evaluated lower blood pressure and cardiovascular and renal outcomes. The Modification of Diet in Renal Disease (MDRD) study was a multicenter clinical trial designed to test the hypotheses that restricting protein intake and controlling BP would delay the progression of chronic kidney disease. The MDRD study consisted of 2 studies. The first study randomized patients with GFR 22–55 mL/ min per 1.73 m^2 to usual protein diet or low-protein diet and to a usual BP defined as MAP ≤107 mmHg or low BP defined as MAP ≤92 mmHg. The projected mean decline in GFR at 3 years did not differ significantly between the protein and blood pressure groups. In study 2, patients with GFR 13–24 mL/min per 1.73 m^2 were assigned to low-protein diet or very-low-protein diet and usual BP defined as MAP ≤107 or low BP defined as MAP ≤92. In study 2, the very-low-protein group has a marginally slower decline in GFR but no delay in the time to occurrence of ESRD or death [12].

The African American Study of Kidney Disease and Hypertension (AASK) trial randomized African Americans with hypertension, age 18–70 years old with GFR 20–65 mL/min per 1.73 m^2, and no other identified causes of renal insufficiency to one of the two mean arterial pressure goals, 102–107 mmHg or <92 mmHg, and to initial treatment with one of the three antihypertensive study drugs, metoprolol, ramipril, or amlodipine. The primary outcome measure was rate of change of GFR. Main secondary outcome was composite index of three clinical endpoints including reduction of GFR of >50 % or 25 mL/min/1.73 m^2, ESRD, or death. The study did not find a significant difference in primary or secondary outcomes or CV events or mortality between the two blood pressure groups [13].

Ramipril efficacy in nephropathy 2 (REIN-2) is a multicenter, randomized controlled trial of patients with nondiabetic kidney disease and proteinuria >1 g/day receiving ramipril 2.5–5 mg/day which randomly assigned them to either conventional BP defined as diastolic BP <90 mmHg or intensive BP control defined as BP <130/80 mmHg using add-on therapy with felodipine 5–10 mg/day. The systolic BP difference between the conventional and intensive BP groups was 4.1 mmHg and diastolic BP difference was 2.8 mmHg. The study showed no difference in ESRD rate between the two BP groups [14] In summary, there is good evidence from the MDRD, AASK, and REIN-2 trials that aggressive BP control is not protective in regard to cardiovascular, renal, or mortality outcomes.

Once BP goals have been identified, aim should focus on the appropriate treatment plan to achieve that goal. Lifestyle modifications should be encouraged in all patients with CKD to lower BP and improve long-term cardiovascular and renal outcomes. KDIGO guidelines on lifestyle modifications are listed in Box 4.

Attainment of blood pressure goal generally requires multiple antihypertensive agents. A number of trials have shown that ACE inhibitors or ARBs can slow the progression of diabetic kidney disease with overt nephropathy. A meta-analysis performed by Jafar *et al.* that included 11 randomized controlled trials comparing the efficacy of ACE inhibitors to other antihypertensive regimens that did not contain ACE inhibitors in nondiabetic patients with kidney disease showed that ACE inhibitors decreased blood pressure and urinary protein excretion, as well as slowed the increase in creatinine and reduced the incidence of ESRD. The benefit was greater

Box 4. What the guidelines say you should do: lifestyle and pharmacologic treatments for lowering blood pressure in non-dialysis-dependent CKD patients [10].

- Individualize BP targets and agents according to age, coexistent cardiovascular disease and other comorbidities, risk of progression of CKD, presence or absence of retinopathy (in CKD patients with diabetes), and tolerance of treatment [not graded]
- Inquire about postural dizziness and check for postural hypotension regularly when treating CKD patients with BP-lowering agents [not graded]
- Encourage lifestyle modification in people with CKD to lower BP and improve long-term cardiovascular and other outcomes
- We recommend achieving or maintaining a healthy weight (BMI 20–25) (1D)
- We recommend lowering salt intake to <90 mmol (<2 g) per day of sodium (corresponding to 5 g of sodium chloride), unless contraindicated (1C)
- We recommend undertaking an exercise program compatible with cardiovascular health and tolerance, aiming for at least 30 min 5 times per week (1D)
- We suggest limiting alcohol intake to no more than two standard drinks per day for men and no more than one standard drink per day for women (2D)

in patients with higher levels of proteinuria [15]. The benefit of ACE inhibitors or ARBs on patients without proteinuria is unknown. KDIGO recommends ARBs or ACE inhibitors as first-line therapy in all CKD patients with albuminuria >300 mg/24 h.

ACE inhibitors generally reduce proteinuria by 30–35 %. The anti-proteinuric effects are generally enhanced when the patient is on a low-sodium diet or taking a diuretic since glomerular microcirculation is more dependent on angiotensin II in relative volume depletion states.

Although ACE inhibitors and ARBs may be particularly beneficial in patients with CKD as noted above, the side effects of these medications, including hyperkalemia, hypotension, and reduction in GFR, make them difficult to use in patients with CKD. Patients who become volume depleted are particularly susceptible to reduction in GFR while taking an ACE inhibitor or ARB. In response to low perfusion pressures, angiotensin II causes increased resistance at the efferent arteriole in an attempt to preserve intraglomerular pressure. This compensatory mechanism is blocked by ACE inhibitors and ARBs. Patients with reduced GFR are more susceptible to elevated potassium levels due to impaired excretion; reducing aldosterone secretion with ACE inhibitors or ARBS blocks the major hormonal stimulus for urinary potassium excretion leading to increased susceptibility to hyperkalemia in patients with CKD. Patients should have their blood pressure, potassium, and creatinine monitored within 1–2 weeks after initiating ACE inhibitor or ARB therapy. Patients at increased susceptibility for adverse effects include elderly patients and those with heart failure, potassium levels >5 mmol/L, advanced CKD with GFR <30 mL/min/1.73 m^2, or on high-dose diuretics. Termination of ACE inhibitors should occur if there is a dramatic increase in serum creatinine concentration from the baseline value within the first few weeks of initiation of therapy or if patient experiences uncontrolled hyperkalemia or any other significant adverse effect.

Despite the benefit of ACE inhibitors and ARBs in previous studies, progression of CKD still occurred in a significant number of patients. Based on this finding, combination blockade of the RAAS has been evaluated in several studies to determine if dual therapy can provide additional benefit. The Aliskiren Trial in Type 2 Diabetics Using Cardiorenal Endpoints (ALTITUDE) was an international, randomized, double-blind, placebo-controlled, parallel group study which randomized a large number of type 2 diabetic patients with renal impairment to receive aliskiren 300 mg daily, a direct renin inhibitor, or placebo in addition to conventional therapy with ACE inhibitor or ARB. The study was terminated early due to lack of benefit of aliskiren over placebo in reducing cardiovascular or renal endpoints after approximately 2 years but an increased risk of adverse events including hypotension, hyperkalemia, and renal impairment [16].

"Kidney Disease: Improving Global Outcomes (KDIGO)" recommends angiotensin II receptor blockers (ARBs) or angiotensin-converting-enzyme (ACE) inhibitors as first-line therapy in all CKD patients with albuminuria >300 mg/24 h.

The VA NEPHRON-D trial was a recently terminated multicenter, prospective, randomized, double-blind clinical trial to assess the effect of combination losartan and lisinopril compared with losartan alone, on the progression of kidney disease in diabetic patients with overt proteinuria. Those randomized to combination therapy had more adverse events leading to early termination of the trial. Publication is pending [17].

Although ACE inhibitors or ARBs are considered first-line therapy in most patients with proteinuric kidney disease, there are no specific guidelines regarding second and third agents used to control blood pressure in CKD patients. Volume expansion often plays a role in hypertensive CKD patients. Higher doses of diuretics are typically required in CKD patients due to the reduction in kidney function. There is some data that taking at least one antihypertensive at night may improve BP control in CKD patients as many are "nondippers," which is one of the strongest predictors of adverse cardiovascular outcomes. When treating hypertension in CKD patients, it is most important to individualize therapy.

Resistant HTN

According to the definition endorsed by the American Heart Association, resistant hypertension is defined as blood pressure that remains above goal (such as 140/90) in spite of the concurrent use of 3 antihypertensive agents of different classes. Ideally, one of the three agents should be a diuretic and all agents should be prescribed at optimal doses. The definition also includes patients with normal or elevated BP in the setting of four or more antihypertensive agents [18].

Resistant hypertension is common and the prevalence is increasing. It is seen among 15–30 % of treated hypertensive patients. Older age, obesity, chronic kidney disease, and diabetes are the strongest predictors of resistant hypertension.

Before diagnosing a person with resistant hypertension, pseudoresistance must be excluded. Pseudoresistance is defined as BP above goal in clinic but below goal outside of the clinic, frequently from white coat hypertension. De Nicola prospectively studied 436 hypertensive CKD patients to determine the prevalence and prognostic role of resistant hypertension in chronic kidney disease patients. The study showed that patients with true resistant hypertension were at high risk for cardiovascular and renal events; however, pseudoresistance in CKD patients is also frequent and does not increase the cardiorenal risk [3].

The best way to exclude pseudoresistance is with home blood pressure or ambulatory blood pressure readings. Home blood pressure monitoring has been shown to be useful in predicting target organ damage, CVD mortality, and CVD events. If the home BP is >135/85 mmHg, there is high probability that the ambulatory blood pressure will also be high and treatment should be started. If home BP is <125/76 mmHg, then a patient may be considered a true normotensive and no ambulatory BP is needed. The gray zone between 125–135 mmHg systolic and 76–85 mmHg diastolic requires further evaluation with ambulatory BP [7]. Agarwal and Andersen found that in patients with CKD, ambulatory blood pressures are a stronger predictor of ESRD or death compared to blood pressures obtained in the clinic [19] (Box 5).

Once true resistant hypertension is diagnosed, a complete history, physical examination, and laboratory studies should be done to look for contributing factors, as the etiology of resistant hypertension is commonly multifactorial. A careful history focusing on lifestyle factors such as physical activity, dietary salt intake, and heavy alcohol intake should be performed. Sodium restriction can lower blood pressure and enhance the anti-proteinuric effects of drugs that block the renin-angiotensin system in patients with

Box 5. What the guidelines say you should do: home and ambulatory BP monitoring [7].

Technical Aspects of BP Measurement
- No tobacco or caffeine for 30 min preceding measurement
- After 5 min of rest
- With arm at heart level; back supported and feet flat on the ground
- On nondominant arm (or arm with highest BP)

BP Monitor
- Use a fully automated device with an upper arm cuff that has been validated by British Hypertension Society, Association for the Advancement of Medical Instrumentation, or International Protocol for the Validation of Automated BP

Measuring Devices
- Monitors with memory that are able to store measurements are preferred

Training of Patients
- Patients should be trained by their healthcare provider, and the monitor readings should be checked against mercury
- Education content: hypertension and cardiovascular risk, BP measurement procedure, use of a validated monitor, cuff size, protocols for measuring BP, interpretation of BP readings, and monitor for their use only
- Reevaluate patient technique and accuracy of the device annually

Target BP Goal
- 135/85 mmHg or 130/80 mmHg if patient has diabetes, coronary heart disease, or chronic kidney disease

Frequency and Schedule of Measurement

Initial values (when patients begin HBPM at home):
- Base decisions on a 7-day measurement period with 2–3 measurements each morning and 2–3 measurements in the evening at prestipulated times (an average of 12 morning and evening values)
- Exclude the first day measurements from the analyses; take advantage of these values as the reference parameter in the subsequent dose-titration phase

Dose-titration phase (titration of initial dose and adjustment therapy):
- All measurements should be made under identical conditions and at the same times of the day and the initial values
- HBPM data should be ascertained as trough values (i.e., before medication taken) in the morning and again at night
- Use the average of BPs measured after 2–4 weeks to assess the effect of treatment

Long-term observation:
- For stable normotensive (controlled) patients, patients should conduct HBPM a minimum of 1 week per quarter (an average of 12 morning and evening measurements under conditions described above)
- Measurement should be made more frequently in patients with poor compliance.

Before you finish: practice pearls for the busy clinician.

- There is a strong association between hypertension and ESRD; however, the cause and effect relationship remains debated especially with the recent discovery of specific genes associated with kidney disease.
- The gold standard for diagnosing renal artery stenosis is renal arteriography. However, less invasive screening tests such as duplex Doppler ultrasonography, CTA, or MRA are typically performed first.
- There are no definitive randomized controlled trial data to guide clinicians on specific antihypertensive medical therapies in patients with renal artery stenosis. Despite previous RCT, whether revascularization is beneficial remains unclear. The CORAL trial may provide more data regarding this topic.
- BP goals should be individualized.
- Evidence supports a goal blood pressure ≤140/90 mmHg for CKD patients without proteinuria defined as albuminuria <30 mg/24 h, regardless of diabetes status.
- Since proteinuria has been associated with worse kidney outcomes, stricter BP control is recommended with goal BP ≤130/80 mmHg in both diabetic and nondiabetic patients with albuminuria >30 mg/24 h.
- Home blood pressure and ambulatory blood pressure monitoring should be used to make an accurate diagnosis of resistant hypertension.
- Treatment of resistant hypertension is typically multifactorial and should focus on a detailed history including lifestyle factors and contributing medications, physical examination, and evaluation for secondary causes of hypertension.

proteinuria. Patients should be educated on interpreting food labels and should be provided feedback by assessing their sodium intake with a 24 h urine collection. Elderly, African Americans, and patients with CKD are particularly salt-sensitive.

A complete medication history is essential as many classes of drugs increase blood pressure including NSAIDS, erythropoietin, oral contraceptives, sympathomimetic agents such as decongestants or diet pills, stimulants, cyclosporine, and natural licorice. Physical examination and laboratory evaluation may reveal signs of organ damage such as retinopathy, cardiovascular disease, or kidney disease.

Box 6. Relevant guidelines.

- KDIGO Clinical Practice Guidelines for the Management of Blood Pressure in Chronic Kidney Disease available at: http://kdigo.org/home/guidelines/blood-pressure-in-ckd/
- ACC/AHA 2005 Practice Guidelines for Management of Patients with Peripheral Arterial Disease (Lower Extremity, Renal, Mesenteric, and Abdominal Aorta) available at: http://circ.ahajournals. org/content/113/11/e463.full.pdf

As part of their complete evaluation, patients with resistant hypertension should be screened for secondary causes of hypertension. CKD and obstructive sleep apnea are the two most common causes of secondary hypertension. Other causes include primary aldosteronism, pheochromocytoma, Cushing's syndrome, and renal artery stenosis.

Even after addressing lifestyle factors, contributing medications, and secondary causes of hypertension, patients often require multiple antihypertensive agents to control blood pressure. There is relatively little data addressing the efficacy of specific combinations of 3 or more drugs. In general, patients with resistant hypertension often have occult volume overload and diuretics may be particularly beneficial and are often underused. Aldosterone antagonists may provide significant antihypertensive benefit when added to other antihypertensive agents in patients with resistant hypertension. This effect may be due to lowering the elevated plasma aldosterone levels in these patients; however, the antihypertensive effect has also been seen in patients with normal aldosterone levels. In addition, spironolactone has anti-proteinuric effects. However, extreme caution must be used when treating patients with resistant hypertension with aldosterone antagonists. These patients are at increased risk for hyperkalemia especially if they also have CKD and/or are also taking an ACE inhibitor or ARB. Given the lack of strong data, combination regimens should be chosen based on prior benefit, adverse events, comorbidities, and financial limitations.

References available on request
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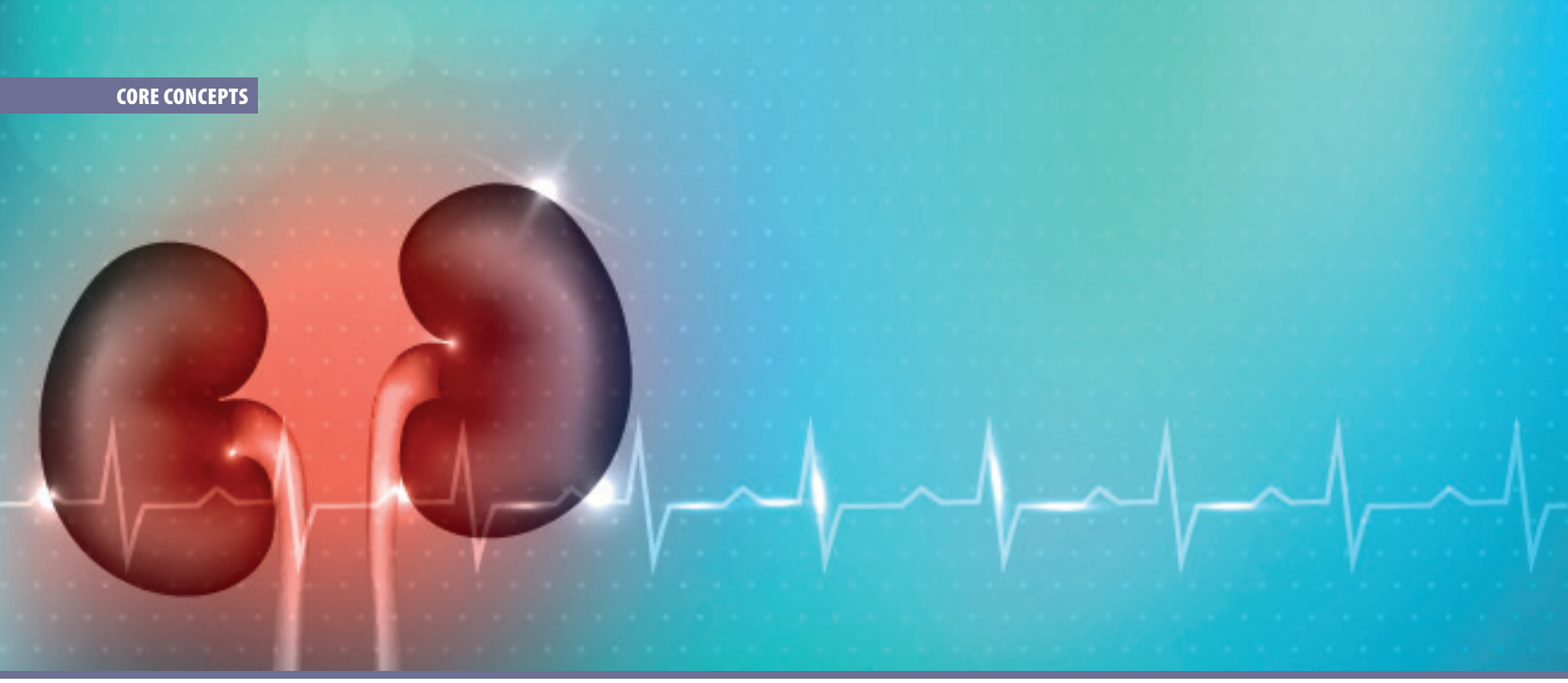
Source: Stephanie Riggen, Rajiv Agarwal. Hypertension and chronic kidney disease. In: M. Arici (ed.). Management of Chronic Kidney Disease. Berlin: Springer-Verlag; 2014, pp. 57–69. DOI 10.1007/978-3-642-54637-2_5.



Cardiorenal continuum

J.A. García-Donaire, L.M. Ruilope

Cardiovascular diseases (CVDs) are a leading cause of death and serious morbidity or disabilities worldwide, and CV events rarely occur in patients without underlying disease; rather, they typically take place as the final stage of a pathophysiological process that results in progressive vascular damage. This stage is called the cardiorenal continuum. This paper discusses cardiorenal continuum and the knowledge regarding the therapeutic interventions that are able to intervene along the continuum.

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Atherosclerosis underlies the vast majority of vascular conditions that are a leading cause of death and serious morbidity or disabilities worldwide. Cardiovascular events rarely occur in patients without underlying disease; rather, they typically take place as the final stage of a pathophysiological process that results in progressive vascular damage, including vital organ damage – specifically, the kidney and the heart. A large percentage of patients attended at the clinic and admitted to hospital have various degrees of heart and kidney dysfunction. Disorders affecting one of them mostly involve the other. Such interactions represent the pathogenesis for a clinical condition called cardiorenal syndrome. Renal and cardiovascular diseases share the same etiopathogenic risk factors. If these factors are controlled, then atherosclerotic process evolution and further target-organ damage or cardiovascular events can be prevented. As the cardiorenal process advances, atherosclerotic vascular damage progresses, and subclinical organ damage can be detected. Chronic kidney disease is included at this stage, and a number of conditions associated with renal dysfunction become novel risk factors that may accelerate vascular damage.

Introduction

Hypertension is a highly prevalent risk factor that affects a large population worldwide [1, 2]. It promotes the development of coronary artery disease (CAD), stroke, renal and peripheral vascular disease, and largely contributes to increased cardiovascular disease (CVD) morbidity and mortality [3]. Regardless of the widespread knowledge about hypertension, the underlying mechanisms that contribute to the most common form of hypertension – essential hypertension – remain unclear, and individuals at the highest risk of developing hypertension must be identified in order to improve their CV status. Diverse studies support a basic role for the kidneys in the pathogenesis of essential hypertension. Cowley and Roman [4] reviewed six lines of evidence that show that renal dysfunction accompanies the development of all forms of hypertension in animal models. They

described abnormal renal sodium excretion as one of the initial findings.

Adequate excretion of an increased sodium load due to high salt intake requires an elevation in glomerular pressure that, when maintained, can potentially lead to glomerular scarring and endothelial dysfunction. Frequently, a phase of glomerular hyperfiltration is observed in the early stage of arterial hypertension and diabetes. This phase can be followed by progressive renal damage with development of chronic kidney disease (CKD), to which a lower than normal number of nephrons at birth could contribute. Scarce data about the contribution of glomerular hyperfiltration to hypertension in humans are available, but during this phase of glomerular hyperfiltration, or later in patients with arterial hypertension and/or diabetes, microalbuminuria can develop [5]

CVDs are a leading cause of death and serious morbidity or disabilities worldwide, and CV events rarely occur in patients without underlying disease; rather, they typically take place as the final stage of a pathophysiological process that results in progressive vascular damage. This stage is called the cardiorenal continuum [6]. Fig. 1 displays an overview of the cardiorenal continuum, illustrating a simplified version of the sequential occurrence of the atherosclerotic process from the first stage, in which CVD risk factors are detected and can be prevented if the conditions are appropriately controlled by implementing the optimal therapeutic approaches

Renal and CV diseases share the same etiopathogenic risk factors, including hypertension, dyslipidemia, glucose metabolism disturbances, cigarette smoking, obesity, and physical inactivity. If these factors are controlled, then atherosclerotic process evolution and further target-organ damage (TOD) or CV events can be prevented. Therefore, prevention can be carried out not just at the first stage but along the whole continuum. As the cardiorenal process advances, atherosclerotic vascular damage progresses, and subclinical organ damage can be detected. This is an intermediate stage in the continuum of vascular disease and a determinant of overall CVD risk. CKD is included at this stage, and a number of conditions associated with renal function decline, such as anemia, secondary hyperparathyroidism, or accumulation of atherogenic substances, become new CVD risk factors and accelerate vascular disease.

CV events rarely occur in patients without underlying disease; rather, they typically take place as the final stage of a pathophysiological process that results in progressive vascular damage. This stage is called the cardiorenal continuum.

Therapeutic approaches at this point can regress CV damage, as shown in the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study, in which reduced urinary albumin/creatinine ratio (UACR) and regression of left ventricular hypertrophy (LVH) was associated with lower incidence of CV events [7]. Therefore, strict objectives regarding CVD risk factors must be set up. A large body of evidence is now available concerning the crucial role of TOD in determining the CVD risk of individuals with and without hypertension. If regression of CV damage is not achieved, the process advances to the development of CV events and progression of CKD to overt nephropathy and CVD. Although prevention strategies must be present along the continuum, interventions at this point should only retard the occurrence of CV and renal events [8]. This last stage represents the situation of further progression of vascular disease, leading to the appearance of symptomatic TOD (myocardial infarction, angina, stroke, transient ischemic attack, advanced chronic renal failure, and peripheral artery disease), which eventually will lead to end-stage renal disease (ESRD) or death. At this stage, the best we can do is to retard the likelihood of such events.

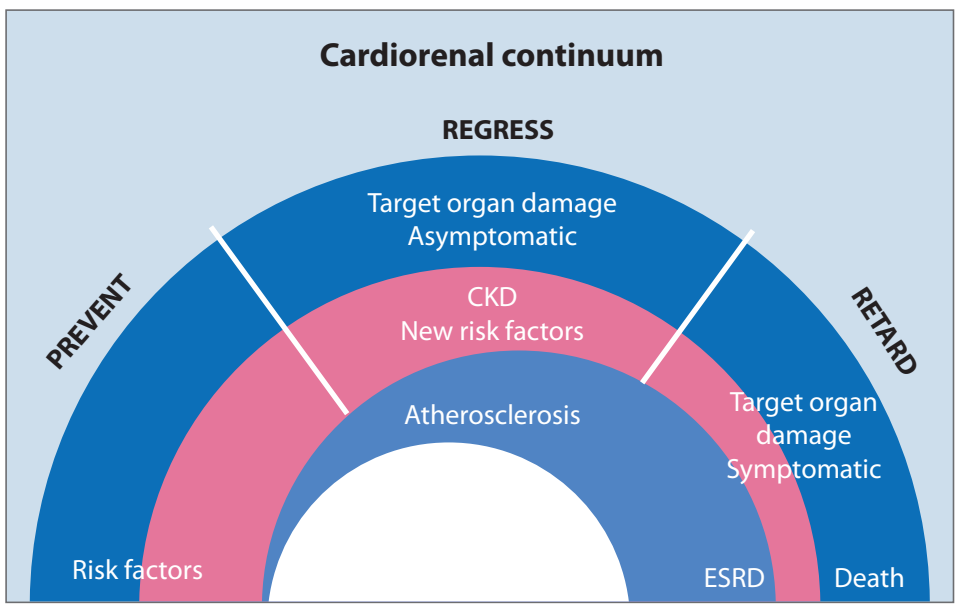

Fig. 1: Cardiorenal continuum.

Cardiovascular disease associated with renal disease: evidences along the continuum

Underlying the cardiorenal continuum is the pathophysiological continuum, which describes the progressive processes at molecular and cellular levels that manifest as clinical disease. A vast amount of research over the last two decades has provided considerably more knowledge regarding the therapeutic interventions that are able to intervene along the continuum.

Therefore, as CVD risk factors can be evaluated, the process begins. At this first stage of cardiorenal disease, preventative approaches are the most relevant strategies to disrupt disease progression [9]. In this sense, some data have demonstrated that high-risk patients without evidence of renal damage may benefit from early therapeutic intervention. The multicenter, double-blind, randomized Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) assessed whether pharmacological intervention could prevent microalbuminuria in high-risk patients with no evidence of organ damage. The main results showed that intervention decreased the incidence of microalbuminuria [10]. Evidence from other ongoing trials will shed light on this issue, as will the Randomised Olmesartan And Diabetes Microalbuminuria Prevention (ROADMAP) study–a placebo-controlled, multicenter, double- blind, parallel group study investigating the effect of the angiotensin receptor blocker (ARB)

olmesartan medoxomil on the incidence of microalbuminuria in hypertensive people with type 2 diabetes and an objective of blood pressure <130/80 mmHg. In addition, ROADMAP will also analyze effects of olmesartan medoxomil on retinopathy and other microvascular circulations [11]. The results of the Diabetic Retinopathy Candesartan Trials (DIRECT) are designed to examine primary (incidence) and secondary (progression) prevention of diabetic retinopathy when blocking angiotensin II type 1 receptors with the ARB candesartan in patients with normoalbuminuric, normotensive type 1 diabetes, and secondary prevention only in patients with normoalbuminuric, normotensive, or treated hypertensive type 2 diabetes. This trial series will also support prevention strategies to block advancement of the atherosclerotic process that leads to development of CV damage [12].

Optimal management in people with several risk factors is crucial, especially when hypertension is associated with other conditions. Awareness that several antihypertensive agents may exert undesirable metabolic effects has antihypertensive treatment trials to investigate the incidence of new-onset diabetes. Almost all such trials with new-onset diabetes as an endpoint have shown a significantly greater incidence in patients treated with diuretics and/or beta-blockers compared with angiotensin-converting enzyme inhibitors (ACEIs), ARBs, or calcium antagonists [13–16]. Angiotensin receptor antagonists [17] and ACEIs [13] have been shown to be associated with significantly fewer new diabetes cases than were calcium antagonists. The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) is comparing telmisartan, ramipril, and their combination for preventing CVD morbidity and mortality in high-risk patients [18]. Telmisartan was the ARB selected for the ONTARGET Trial because it provides sustained antihypertensive activity over the 24-h between doses [19]. The comparator, the ACEI ramipril, was selected because in the Heart Outcomes Prevention Evaluation (HOPE) trial, ramipril was proved to reduce the incidence of CV events in a similar patient population [20]. Patients enrolled in ONTARGET have vascular disease (coronary artery disease, peripheral arterial occlusive disease, stroke) or diabetes with TOD. The primary outcome is a composite endpoint of CVD, death, stroke, acute myocardial infarction, and hospitalization for congestive heart failure (CHF). A variety of renal endpoints have also been included. The Telmisartan Randomized Assessment Study in ACE-I-Intolerant Subjects with CV Disease (TRANSCEND) is a parallel study within the ONTARGET Trial that is comparing the CV protective effect of telmisartan with placebo in patients intolerant of ACEIs [18]. The first results of this trial have been published and emphasize that the telmisartan was equivalent to ramipril in treating patients with vascular disease or high-risk diabetes and was better tolerated [21]. The combination of these two drugs was associated with more adverse events without an increased benefit. More evidence about prevention along the cardiorenal continuum is expected from this trial, including more than 150,000 patient-years of data. The Trial of Preventing Hypertension (TROPHY) hypothesized that early treatment with candesartan might prevent or delay hypertension onset. The main results showed that candesartan was better in preventing development of hypertension versus placebo [22]. The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) evaluated the benefits associated specifically with the use of statins among patients with hypertension [23]. Atorvastatin, which was added to the treatment therapy in more than10,000 patients with hypertension and additional CVD risk factors and a serum total cholesterol <6.5 mmol/L, reduced serum total cholesterol by 19.9% compared with placebo. This was accompanied by substantial benefits both with regard to total CV and renal events (36% reduction) and stroke (27% reduction). The Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial was recently terminated prematurely because the predefined efficacy outcome was achieved and an interim analysis reported. The trial recruited more than 11,400 patients who received either amlodipine in combination with benazepril or hydrochlorothiazide in combination with benazepril. A primary composite endpoint of CVD morbidity or mortality was defined as death from CV causes, fatal or nonfatal myocardial infarction or fatal or nonfatal stroke, revascularization, or unstable angina requiring hospitalization. Treatment with amlodipine/benazepril significantly reduced CVD morbidity and mortality compared with hydrochlorothiazide/ benazepril [relative risk (RR) 0.80; 95% confidence interval (CI) 0.71–0.90] [24]. Mechanical and chemical damage resulting from these interrelated CVD risk factors promote general progression of vascular damage that begins with endothelial dysfunction and atherosclerosis. This leads to end-organ damage, such as LVH, subclinical atherosclerotic vascular damage, and kidney injury that can be detected by microalbuminuria and renal function derangement [estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 or a slight increase in serum creatinine]. At this second stage, vascular damage processes may be regressed, and inhibition of the renin–angiotensin system (RAS) has been shown to be the most efficient pharmacological intervention along with strict control of CVD risk factors.

The diagnosis of hypertension-induced renal damage in a hypertensive patient is usually based on reduced renal function and/or elevated urinary excretion of albumin.

International guidelines devoted to arterial hypertension recognize microalbuminuria, elevated serum creatinine values, and reduced eGFR as major CVD risk factors that contribute to increased risk afforded by other coexisting factors [25–27]. The diagnosis of hypertension-induced renal damage in a hypertensive patient is usually based on reduced renal function and/or elevated urinary excretion of albumin. Renal function decline is classified in accordance with eGFR calculated by the abbreviated Modification of Diet in Renal Disease (MDRD) formula that assesses age, gender, race, and serum creatinine [28]. Values of eGFR <60 ml/min/1.73 m^2 indicate CKD stage 3, whereas values <30 and 15 ml/min/1.73 m^2 indicate CKD stages 4 and 5, respectively [29]. The Cockcroft–Gault formula estimates creatinine clearance (CrCl) and is based on age, gender, body weight, and serum creatinine [30]. This formula is applicable in the range >60 ml/min, but it overestimates CrCl in CKD stages 3–5 [31]. Both procedures help to detect mildly impaired renal function in the face of serum creatinine values that are still in the normal range.

Reduction in GFR and increase in CVD risk may also be inferred from

increased serum levels of cystatin C [32]. Whereas elevated serum creatinine concentration or low eGFR (or CrCl) points to reduced rate of plasma filtered at the glomerular level, increased urinary albumin or protein excretion points to derangement in the glomerular filtration barrier, which allows increased albumin passage. Microalbuminuria has been shown to predict the development of overt diabetic nephropathy in those with either type 1 or type 2 diabetes [33]. However, only about 40% of those with type 2 diabetes will develop microalbuminuria and, of those, approximately 50% will develop microalbuminuria in the following 10 years [34]. In contrast, in both diabetic and nondiabetic hypertensive patients, microalbuminuria, even below the threshold values currently considered [35], has been shown to predict CV events. Several studies report a continuous relationship between CVD – as well as non-CVD – mortality and urinary protein/creatinine ratios >3.9 mg/g in men and 7.5 mg/g in women [36]. Thus, the term "microalbuminuria" may be misleading (because it falsely suggests a minor injury as well) and should, in theory, be replaced by the term "low-grade albuminuria" [37]. Microalbuminuria can be determined in spot urine samples (24-h or night-time urine samples are discouraged due to inaccuracy of urinary sampling) by indexing the urinary albumin concentration to the urinary creatinine concentration. Initial evidence concluding that microalbuminuria increases CVD risk came from observations involving high-risk patients [38]. Data from the HOPE study [39] confirmed the predictive value of microalbuminuria, which attained a predictive capacity similar to that of previous coronary artery disease and was equal for patients with and without accompanying diabetes. The relevance of urinary albumin excretion (UAE) as a CVD risk factor in patients with hypertension without diabetes and in the general population has also been demonstrated [40]. Some of these studies indicate that the relationship between urinary albumin and CVD risk is a continuum that starts below the established cutoff point indicated earlier. Definitely, both UAE and reduced GFR are independently associated with increased CVD risk, which is particularly elevated when both alterations coexist [41]. In fact, the prevalence of albuminuria, either micro or macro, increases as eGFR falls <60 ml/min/1.73 m^2 [42].

Patients developing ESRD are a minority in the group developing different forms of CKD. They could be considered survivors because CVD accounts for the majority of deaths of patients with CKD before the development of ESRD [43]. In turn, advanced CVD facilitates the development of CKD, and so the relationship between CKD and CVD becomes a vicious circle. That CKD and CVD are so closely related has resulted in increased interest in investigating the evolution of renal function in trials involving patients with hypertension, as well those with heart failure and postmyocardial infarction. This interest is fully justified, as in all these situations, renal function alterations are predictive for the development of CV events or death.

Left ventricular hypertrophy (LVH) is common in patients with renal insufficiency even before they progress to dialysis, and so prevalence of LVH correlates with the degree of renal functional deterioration.

Even from the early stages, CKD adds to CVD risk in any patient with hypertension and in any patient presenting with established forms of CVD [44]. Reduction of CV events in the CKD population requires the implementation of effective integral therapeutic interventions that protect both the kidney and the CV system. These interventions have to be implemented in the very initial stages of CKD, and strict blood pressure control is imperative in any patient with an elevated global CVD risk and high blood pressure. In the absence of other CVD risk factors, elevated blood pressure levels are required in order to consider patients as having high added CVD risks. In contrast, only high–normal blood pressure levels or even lower values are required for the same evaluation when patients present with three or more associated CVD risk factors, TOD, diabetes, or associated clinical conditions. Accordingly, patients with hypertension and a high added level of CVD risk can be found in any of the three stages of the CV and renal disease continuum. As soon as renal function exhibits minor derangements, CVD risk continues to increase until ESRD develops.

As renal function declines, TOD appears and CKD adds several clinical characteristics that raise the possibility of a CV event as atherosclerotic disease progresses. CKD-induced anemia and secondary hyperparathyroidism globally worsens outcomes in patients with and without myocardiopathies, and correction of these conditions is crucial to reduce absolute CVD risk [45, 46]. Among patients who referred to the authors' hypertension unit, 7.6% had a decreased renal function according to serum creatinine levels, and 25% had a decreased CrCl [47]. Community-based longitudinal studies demonstrated that CKD is an independent risk factor for the composite study outcome, including myocardial infarction, fatal CHF, stroke, and death [48]. In patients with essential hypertension and normal renal function (defined as eGFR >90 ml/min/1.73 m^2), those who developed CKD during 13 years of follow-up had a CV event rate 2.5 times higher than did those with preserved renal function [49]. As widely evidenced in the hypertensive population, the higher the CVD risk, the higher the CKD prevalence [50].

Evidence for the relationship between renal dysfunction and adverse CV events was initially documented in the ESRD population in whom the incidence of CVD death is elevated. Around 50% of individuals with ESRD die from a CVD – a CVD mortality rate much higher than the age-adjusted CVD mortality rate in the general population. This discrepancy is present across all ages, but it is most marked in the younger age group, in which the CVD mortality rate is >300-fold in ESRD patients compared with age-matched controls with normal renal function [51]. By the time ESRD occurs, 40% of patients have evidence of CHF, and 85% of those patients have abnormal LV structure and function.

The relationship between renal disease and CVD mortality has also been shown to extend to patients with more moderate degrees of renal impairment. Indeed, the majority of patients with eGFR <60 ml/min/1.73 m^2 die from CVD-related causes rather than progressing to ESRD. In addition, evidence of structural and functional cardiac abnormalities has been demonstrated. Data about cardiac structure in the renal insufficiency population has been described with echocardiographic techniques and comparable criteria for diagnosing LVH, detecting an LVH prevalence of 16% in patients with CrCl of >30 ml/min and 38% in those with CrCl <30 ml/min [52]. Therefore, LVH is common in patients with renal insufficiency even before they progress to dialysis, and so prevalence of LVH correlates with the degree of renal functional deterioration. Many reports have shown that the relationship between renal impairment

and increased CVD mortality rate extends across the spectrum of renal dysfunction to cover the mildest degree of renal disease. Furthermore, this relationship appears to be maintained through populations with broadly diverse degrees of baseline CV health. LVH is an independent predictor of unfavorable prognosis in the hypertensive population, and, in the LIFE study, its relationship with albumin excretion was reported as being independent of age, blood pressure, diabetes mellitus, race, serum creatinine level, or smoking [53]. The prevalence of microalbuminuria was approximately two-fold higher in patients with hypertension and eccentric or concentric LVH and minimally elevated in the group with concentric LV remodelling compared with patients with normal LV geometry. Although the clinical significance of impaired renal function and LVH in patients with hypertension is not yet fully understood, numerous reports link renal albumin leakage with morbidity and mortality.

The LIFE study also showed that the simple measurement of UACR further refines risk stratification by LV geometry and that patients with LVH have an increased risk of also having albuminuria, a situation that should be further investigated to improve treatment and counselling. The risk for CVD endpoints increases in a stepwise trend with higher values for UACR in patients with diabetes. Data indicate that albuminuria at a lower level than that usually used as a cut point in patients with diabetes defines patients at increased risk of CVD morbidity and mortality. UACR did not predict the risk of myocardial infarction. Perhaps diabetes itself is a strong predictor for CVD morbidity and mortality, partly overlapping the influence of albuminuria as a risk factor in the population with rather low levels of albuminuria. Other studies suggest that albuminuria at levels below established values is a risk factor for CHF in patients with and without diabetes, signifying that the relationship between albuminuria and CVD risk from other populations cannot be directly applied to nondiabetic hypertensive patients [54].

Strict control of all CVD risk factors and therapeutic action in order to regress already established vascular damage must be the cornerstone of the medical strategy, because, if not stopped, the cardiorenal continuum progresses to CKD (proteinuria, eGFR <30 ml/min/1.73 m^2), overt CVD, and stroke. Interventions at this point are focused on delayed development of CV and renal events [27]. CV events and consequent death are dramatically reduced when UACR is decreased and GFR decline is avoided. If renal decline progresses to the final stage, proteinuria will occur. In type 2 diabetes, data from the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial showed that changes in albuminuria in the first 6 months of therapy were approximately linearly related to the degree of long-term renal protection: every 50% reduction in albuminuria in the first 6 months was associated with a 45% reduction in the risk for ESRD during later follow-up [55]. Furthermore, a secondary analysis of the Irbesartan in Diabetic Nephropathy Trial (IDNT) demonstrated that the risk for renal failure was reduced during the first year of the study when there were increases in proteinuria [56]. Subsequently, these two studies (IDNT and RENAAL) demonstrated that an ARB (irbesartan or losartan) was more effective than conventional therapy or a calcium channel blocker in slowing progression of nephropathy, regardless of blood pressure control. Moreover, secondary analyses of these two large trials demonstrated that there was some interaction between the effect of the ARB and the levels of blood pressure that were achieved. It can also be concluded that optimal levels of blood pressure tended to magnify the renoprotective effects of ARB in both trials. In the large cohort of patients with hypertension, microalbuminuria, and type 2 diabetes who participated in the Microalbuminuria, Cardiovascular, and Renal Outcomes–Heart Outcomes Prevention Evaluation (MICRO-HOPE), the ACEI compared with other treatments was more effective in reducing the incidence of overt nephropathy [57]. Furthermore, the Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria (IRMA-2) study showed that treatment with the ARB irbesartan was much more effective than conventional therapy at both preventing the development of clinical proteinuria and favoring regression to normoalbuminuria in patients with microalbuminuria and type 2 diabetes, despite similar blood pressure control [58].

Global therapeutic approach focused on renal outcomes

CKD progression, that is, reduced GFR, occurs at a variable rate, with a faster rate of decline generally noted among patients with diabetic nephropathy due to the presence of proteinuria. Several therapeutic options have been shown to be efficient in slowing the rate of renal function decline. Among these therapeutic treatments are blood-pressure-reducing drugs – preferably ACEIs and/or angiotensin II antagonists – low-salt and low-protein diets, and lipid-lowering drugs [59].

Unfortunately, for such treatments to be most efficacious and in agreement with the European Society of Hypertension/ European Society of Cardiology guidelines, it is necessary to identify patients in an early stage of disease before significant loss of renal function has occurred. Such identification is simplified by the estimating GFR and measuring microalbuminuria in any patient with hypertension. UACR levels of approximately >2 mg/g or an estimated excretion rate of 2 mg/day are significantly associated with death from CVD, myocardial infarction, stroke, and elevated blood pressure. As a result, reductions in albuminuria levels during treatment translate to regression of a number of vascular abnormalities in hypertension and thus a decrease in risk in general. In patients type 2 diabetes and diabetic nephropathy, and also in patients with nondiabetic renal disease, data indicate that the extent of decreases in albuminuria during renin–angiotensin–aldosterone system intervention is associated with the degree of renal protection but also the degree of reduced CVD risk [60]. Reductions in both systolic and diastolic blood pressure are important in reducing albuminuria levels. Despite the firm relationship between blood pressure values and albuminuria, ACEIs and ARBs exhibit a more marked capacity to reduce microalbuminuria in patients with hypertension compared with a number of different therapeutic interventions, such as calcium antagonists, beta-blockers, or diuretics [61].

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Coronary computed tomography angiography for screening in patients with diabetes: can enhanced detection of subclinical coronary atherosclerosis improve outcome?

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The incidence of cardiovascular morbidity and mortality among diabetic patients remains high, including in patients with no prior symptoms. This underscores a possible advantage for appropriate screening of asymptomatic patients for the presence of obstructive coronary artery disease (CAD). The present paper reviews a possible role of coronary computed tomography angiography (CCTA) in the screening of asymptomatic diabetic patients for possible obstructive CAD.

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It is well known that there is a very high risk of cardiovascular complications among diabetic patients. In spite of all efforts at aggressive control of diabetes and its complications, the incidence of cardiovascular morbidity and mortality remains high, including in patients with no prior symptoms, underscoring a possible advantage for appropriate screening of asymptomatic patients for the presence of obstructive coronary artery disease (CAD). In this article, we sought primarily to review the results of studies designed to evaluate a possible role of coronary computed tomography angiography (CCTA) in the screening of asymptomatic diabetic patients for possible obstructive CAD. Our review of current literature indicates that there is still no method of CAD screening identified that has been shown to reduce the cardiovascular risk of asymptomatic diabetic patients. Therefore, the utility and value of screening for CAD in asymptomatic diabetic patients remains controversial. CCTA screening has shown promise and has been demonstrated to predict future risk, but as yet has not demonstrated improvement in the outcomes of these high-risk patients. At our present state of knowledge, aggressive risk factor reduction appears to be the most important primary prevention strategy for all asymptomatic high-risk diabetic patients. However, there remains a great need for better and more sensitive and specific screening methods, as well as more effective treatments that may allow us to more accurately target diabetic patients who really are at high risk. Further large randomized and well-controlled clinical trials may be necessary to determine whether screening for CAD can reduce cardiovascular event rates in patients with diabetes.

Introduction

Heart disease remains the leading cause of death in the USA [1]. There are a number of published reports indicating that coronary artery disease (CAD), and associated acute myocardial infarction (MI), is the major cause of cardiovascular morbidity, mortality, and medical costs [1–3]. In addition, although some patients experience premonitory symptoms prior to the actual event, for many patients their first coronary symptom is the MI itself [3].

Diabetes mellitus is an important risk factor for the development and severity of CAD. Diabetes is defined as "a group of diseases marked by high levels of blood glucose resulting from problems in how insulin is produced, how insulin works, or both" [2]. Understandably, diabetes impacts multiple organ systems, and a broad spectrum of serious complications can develop in people who have diabetes [2]. These complications include blindness, nerve disease, hearing loss, gum disease, erectile dysfunction, kidney failure, fatty liver disease, depression, complications of pregnancy, stroke, heart disease, and premature death. In the last decade, diabetes was the seventh leading cause of death in the USA [1].

Diabetes and cardiovascular complications

It is well known that there is a high risk of cardiovascular complications among diabetic patients. [4]. Individuals with diabetes are also more likely to develop severely obstructive, yet asymptomatic, CAD [5]. Often, diabetic patients remain completely asymptomatic up to the point when they first have a major event, like an acute MI. The Centers for Disease Control report that 34 % of all cardiovascular deaths occur in diabetic patients that have no prior symptoms [2]. Because of the combination of aggressive atherogenicity and asymptomatic presentation, CAD is the most common cause of death in both

non-insulin-dependent diabetes (all ages) [6] and insulin-dependent diabetes (after 30 years) [7].

Lifestyle interventions that lead to weight loss and increased physical activity have been shown to delay the onset of diabetes, as reported in a major randomized clinical trial of people at high risk for diabetes [8]. This study also showed that in some cases, such interventions returned blood glucose levels to within the normal range. Aggressive care to reduce risk factors in people with diabetes is recommended by the American Diabetes Association, including diet and weight management, exercise, aspirin use, and treatment targets of systolic BP < 120 mmHg, LDL-C level < 70 mg/dL, HDL-C level > 50 mg/dL, triglyceride < 150 mg/dL, and HbA1c<6.5 % [9].

In addition to lifestyle interventions and aggressive medical therapy, coronary revascularization has been recommended per national guidelines for improving survival in severe CAD patients. However, the results of two large clinical trials, Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) [10] and Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) [11], have raised the question of whether revascularization really provides benefit over optimal medical therapy. In the BARI 2D study, 2368 patients with type 2 diabetes and obstructive CAD were randomly assigned to undergo prompt revascularization with intensive medical therapy or to intensive medical therapy alone [10]. Further, patients were stratified to undergo insulin-sensitization or insulin-provision therapy and were followed over 5 years. No significant difference was found in the rates of death and major cardiovascular events between patients undergoing prompt revascularization versus those undergoing medical therapy alone, or between strategies of insulin sensitization versus insulin provision. In the COURAGE study, 2287 patients with myocardial ischemia and significant CAD were randomized to percutaneous coronary intervention (PCI) with intensive medical therapy and lifestyle intervention, or to optimal medical therapy alone, and were followed over 4.6 years [11]. There was no significant difference in the composite of death, MI, and stroke, or in hospitalization for acute coronary syndrome or MI, between the PCI and the medical therapy groups.

In spite of all efforts at aggressive control of diabetes and its complications, cardiovascular death occurs in an estimated 300,000 patients with no prior symptoms per year in the USA alone [2]. These statistics emphasize a need to identify effective screening strategies among asymptomatic patients for the presence of obstructive CAD.

Screening for coronary artery disease in diabetic patients

Currently, there are no national guidelines that recommend screening for CAD in any asymptomatic patient population. In fact, the most recent American Diabetes Association guidelines recommend against screening for cardiovascular disease in asymptomatic diabetic patients [12]. The basis for this recommendation is the paucity of data suggesting any specific benefits of invasive interventions over medical therapy alone, and therefore, CAD screening in the asymptomatic patient with diabetes mellitus appears non-beneficial and remains highly controversial.

There are a number of potential reasons, however, why appropriate screening for obstructive CAD may still be beneficial. The identification of asymptomatic CAD via an appropriate and effective screening method could result in more aggressive lifestyle

Currently, there are no national guidelines that recommend screening for CAD in any asymptomatic patient population.

and/or pharmacological interventions and decisions to take earlier actions (e.g., revascularization), and this may significantly reduce the incidence of death and myocardial infarction among the many thousands of diabetic patients in the USA. In addition, there is likely a subgroup of asymptomatic diabetic patients with underlying obstructive CAD severe enough to warrant revascularization to prevent the morbidity associated with CAD, including death, chronic heart failure, and recurrent cardiac arrhythmias. Last, targeted screening may make possible the reduction of overall cardiovascular complications, and thus, the overall cost of managing these patients may also be reduced.

Past attempts at screening asymptomatic diabetic patients have been able to predict which patients were at higher risk of a future CV event, but were not able to demonstrate a change in the adverse clinical outcomes of patients. In the Detection of Ischemia in Asymptomatic Diabetics trial (DIAD), 1123 asymptomatic patients with type 2 diabetes and no symptoms of CAD were randomized to screening with adenosine-stress radionuclide myocardial perfusion imaging versus no screening and followed for 4.8 years [13]. Although the study showed that evidence of CAD in the screening group predicted higher cardiac event rates, the overall cardiac event rates were three- to fourfold lower than expected, and no significant difference in cardiac death or nonfatal MI was found between the screened and not-screened groups. Additionally, the screening group actually received nominally less coronary revascularizations than the control group (5.5 versus 7.8 %, p = 0.14). The cumulative cardiac event rate in this study was 2.9 %, much lower than other studies and/or known registries, e.g., 6 % in the FIELD study (with follow-up period of 5 years) [14], 7 % in the ACCORD study (with follow-up period of 3.5 years) [15], and 12.1 % in the INSPIRE database (ongoing registry for 15.5 years, unpublished data) [16].

Coronary computed tomography angiography

The advent of high-resolution multi-detector coronary computed tomography angiography (CCTA) offers the opportunity to non-invasively evaluate coronary anatomy and determines the presence and extent of coronary atherosclerosis [17]. CCTA is an advanced imaging method that uses a computerized tomography scanner to examine the structure and the blood vessels of the heart non-invasively and painlessly. Specifically, this imaging test can help determine if plaque buildup has narrowed, or in some cases, completely blocked, a patient's coronary arteries. Although functional testing for ischemia is still recommended as the preferred test among symptomatic patients, current guidelines have included CCTA for risk stratification in some patient groups and specific indications. Studies have shown that CCTA accurately identifies the presence and severity of obstructive CAD [18, 19]. In a meta-analysis comparing the diagnostic accuracy and post-test outcomes of CCTA versus

Table 1. Comparison of studies that investigate screening for coronary artery disease.

Year	Study	Design	# pts	Population description	Intervention/ treatment arms	Primary endpoint	Follow-up period (x)	Key findings
2008	CORE-64 study	Prospective multicenter, observational study, seven countries, nine sites	291	Suspected or known CAD (calcium score <600); 68 pts (23 %) with DM	MD CTA vs. conventional coronary angiography	Diagnostic accuracy of MD CTA	30 days	MD CTA accurately identifies the presence and severity of obstructive CAD. AUC 0.93 (95 % CI, 0.90–0.96). Sensitivity 85 % (95 % CI, 79–90). Specificity 90 % (95 % CI, 83–94).
2009	DIAD	RCT, multicenter, 14 sites	1123	Type 2 DM	Grp 1 – CD screening with ASMPI vs. Grp 2 – no screening	Death or non-fatal MI	4.8 years	Overall event rate: 2.91 %, NS between the two groups. Primary events: Grp 1 = 2.7 % vs Grp 2 = 3 %, p = 0.73, 95 % CI, 0.44–1.8. Evidence of CAD predicted higher event rates.
2012	CORE-64 study	Prospective multicenter, observational study, seven countries, nine sites	371	Suspected or known CAD (including calcium score > 600); 97 pts (26.2 %) with DM	MD CTA vs. conventional coronary angiography	Diagnostic accuracy of MD CTA to detect severe obstructive CAD	30 days	CTA is less effective in patients with calcium score >600 and in patients with high pretest probability for obstructive CAD. AUC 0.81 (95 %CI 0.71–0.89, p = 0.077 vs. <600).
2012	ROMICAT-II	RCT, nine sites	1000	Symptoms suggestive of acute coronary syndrome; 173 pts (17 %) with DM	Grp 1 – CCTA vs. Grp 2 – standard evaluation in emergency department	Length of hospital stay (LOS), time to diagnosis, resource utilization, radiation exposure, cumulative costs	28 days	Incorporating CCTA improved efficiency of clinical decision-making, but increased downstream tests and radiation exposure, and did not decrease overall cost of care. LOS: Grp 1 = 23.2 + 37 h, vs. Grp 2 = 30.8 + 28 h, p < 0.001; Time to diagnosis: Grp 1 = 10.4 + 12.6 h, vs. Grp 2 = 18.7 + 11.8 h, p < 0.001; Radiation: Grp 1 = 13.9 + 10.4 mSv, vs. Grp 2 = 4.7 + 8.4 mSv, p < 0.001; Cost: Grp 1 = USD$4289, vs. Grp 2 = USD$4060, p = 0.65.
2014	Nielsen *et al.*	Meta-analysis, 17 studies, 2002–2013	1349 vs. XECG; 2884 vs. SPECT	Suspected stable CAD (pts with DM not indicated)	XECG vs. SPECT vs. CCTA	Diagnostic accuracy and post-test outcomes	3 to 55 months	Diagnostic performance of CCTA is higher than both XECG and SPECT in detecting significant CAD. Sensitivity (95 % CI): CCTA = 98 % vs. XECG = 67 %, p < 0.001; CCTA = 99 % vs. SPECT = 73 %, p = 0.001. Specificity (95 % CI): CCTA = 82 % vs. XECG = 46 %, p < 0.001; CCTA = 71 % vs. SPECT = 48 %, p = 0.14. CCTA associated with increased DTU vs. XECG/SPECT (OR = 1.38, p < 0.001).
2014	FACTOR-64	RCT, treatment trial, single site	900	Type 1 or 2 DM without CAD symptoms	Grp 1 – CCTA CAD screening vs. Grp 2 – optimal care, guideline-based.	Composite of death, MI, unstable angina	4 years	Overall event rate: 2 %. NS between the two groups. Primary events: Grp 1 = 6.2 %, 95 % CI 0.49–1.32, vs. Grp 2 = 5.6 %, 95 % CI 0.41–1.16, p = 0.16. Evidence of CAD predicted higher event rates.
2015	CAPP	RCT, single site	500	Stable chest pain; 26 pts (5.3 %) with DM	XECG vs. CCTA	SAQ scores for evaluation of chest pain	1 year	CCTA improved angina and resulted in fewer investigations and re-hospitalizations. SAQ subscale for angina stability: difference BL to 3 M, mean = −11.1, 95 % CI −17.4 to −4.8, p = 0.001; difference BL to 12 M, mean = −6.8, 95 % CI −12.8 to −0.7, p = 0.028.
2015	PROMISE	Prospective, open-label, randomized, 193 sites	10,003	Low to moderate chest pain; 2144 pts (21.4 %) with DM	Grp 1 – anatomical testing with CCTA vs. Grp 2 – functional testing (XECG, NST or XECHO)	Composite of major CV events within 72 h, i.e., death, MI, unstable angina, complications	2 years	Improved diagnostic performance of CCTA, but no improvement in clinical outcomes. Overall event rate: 3.1 %. Primary events: Grp 1 = 3.3 % vs. Grp 2 = 3.0 %, 95 % CI 0.83–1.29, p = 0.75.
2015	DADDY-D	Prospective, open-label, randomized, single site	520	DM with no known CAD	Grp 1 – standard medical therapy vs. Grp 2 – screening program based on ETT aimed at revascularization (surgical or percutaneous)	Reduction of first cardiac event	3.5 years	No reduction in cardiac events and HF episodes. Cardiac events: Grp 1 = 5.4 %, vs. Grp 2 = 4.6 %, 95 % CI 0.393–1.8727, p = 0.678. HF first occurrence: Grp 1 = 2.7 %, vs. Grp 2 = 0.8 %, 95 % CI 0.057–1.314, p = 0.083.
2016	Diabetic patients ROMICAT-II	RCT, nine sites	1000	DM vs. non-DM, with symptoms suggestive of ACS; 173 pts (17 %) with DM	CCTA vs. standard evaluation in emergency department	Length of hospital stay	28 days	LOS unaffected by CCTA in DM pts (23.9 vs 27.2 h, p = 0.86) but reduced for non-DM pts (8.4 vs. 26.5 h, p < 0.0001). CCTA resulted in high rate of ED discharge in both DM and non-DM groups (40 and 49 % for CCTA vs. 14 and 13 % for standard, each p < 0.0001, p interaction = 0.27).

3 M at 3 months, *12 M* at 12 months, *ACS* acute coronary syndrome, *ASMPI* adenosine-stress myocardial perfusion imaging, *BL* baseline, *CAD* coronary artery disease, *CCTA* coronary computerized tomography angiography, *CI* confidence interval, *DM* diabetes mellitus, *DTU* downstream test utilization, *ED* emergency department, *ETT* exercise tolerance testing, *Grp* group, *HF* heart failure, *MI* myocardial infarction, *MD CTA* multi-detector computed tomographic angiography, *NI* not indicated, *NS* no statistical significance, *NST* nuclear stress testing, *OR* odds ratio, *Pts* patients, *RCT* randomized controlled trial, *SAQ* Seattle Angina Questionnaire, *SPECT* single-photon emission computed tomography, *x* mean, *XECG* conventional exercise electrocardiography, *XECHO* stress echocardiography.

conventional exercise electrocardiography (XECG) and single-photon emission computed tomography (SPECT), Nielsen *et al.* reviewed 11 eligible studies [20]. Their systematic review showed that the up-front diagnostic performance of CCTA is higher than both XECG and SPECT in detecting significant CAD. Their review also showed that CCTA was associated with increased downstream test utilization and coronary revascularization.

The Coronary Artery Evaluation Using 64-Row Multidetector Computed Tomography Angiography study (CORE-64) is probably the most definitive study that describes the potential for CCTA [18•]. This study was conducted in 291 symptomatic patients with suspected CAD who underwent CCTA and calcium scoring (including only patients with calcium score <600 Agatston units) prior to conventional coronary angiography. This study showed a high correlation between CCTA and invasive coronary angiography in the detection of the extent and severity of CAD and subsequent revascularization.

A follow-up CORE-64 study publication looked at 371 patients who underwent CCTA and cardiac catheterization for detection of obstructive CAD, this time including all patients regardless of calcium score [19]. In this study, the inclusion of patients with severe coronary calcification did not alter the overall test performance of CCTA, although the diagnostic accuracy of CCTA was reduced in patients with calcium scores of >600 versus those with scores <600 Agatston units

In another study, Cardiac CT for the Assessment of Pain and Plaque (CAPP), McKavanagh *et al.* randomized 500 patients with symptoms of stable chest pain, to XECG or to CCTA, to determine the symptomatic and prognostic differences between the two assessment modalities, using the Seattle Angina Questionnaire (SAQ) scores for evaluation of chest pain [21]. The CCTA arm had a statistically significant difference in angina stability and quality-of-life domains of the SAQ at 3 and 12 months compared with the XECG arm, suggesting less angina. Further, there were more unplanned hospitalizations and CAD events within the XECG group compared to CCTA, although the overall numbers were low. This study demonstrated that CCTA, as an index investigation for stable chest pain, improved angina symptoms and resulted in fewer investigations and re-hospitalizations compared with the XECG group.

Although these studies demonstrated the diagnostic utility of CCTA for presence and extent of CAD, actually demonstrating a change in adverse clinical outcomes for the patients (e.g., a reduction in cardiac events) requires randomized clinical outcomes trials. In addition, CCTA involves contrast administration, radiation exposure, and significant cost. Therefore, justification of routine screening requires demonstration of benefit in an appropriate high-risk population.

Justification of routine CCTA screening requires demonstration of benefit in an appropriate high-risk population.

Trials evaluating the potential clinical benefit of coronary computed tomography angiography in asymptomatic patients

There are several published randomized trials that have evaluated the use of CCTA in asymptomatic or mildly symptomatic patients (see Table 1). A major study in this population is the recently completed FACTOR-64 trial conducted at Intermountain Healthcare [22]. This randomized clinical trial studied 900 patients without symptoms of CAD and with >12 years average duration of type 1 or 2 diabetes who were subsequently followed for 3 to 5 years. The study objective was to determine if routine CCTA screening of asymptomatic patients with diabetes, compared to a no-screening control group of asymptomatic patients with diabetes treated with optimal guideline-directed medical therapy, could change how these patients are cared for and beneficially influence clinical outcomes and risk factor control. A unique aspect of this study is that patients in the screening arm were cared for by their primary care physicians according to recommendations based on the CCTA screening results, which included more aggressive medical management, further cardiac stress testing, or coronary angiography, and coronary revascularization therapy in patients deemed likely to benefit from it. This study showed that among asymptomatic patients with diabetes, many of whom were found by CCTA to have large amounts of coronary atherosclerosis present, changes in medical care, that were instituted as a result of the CCTA screening for CAD, did not reduce the rate of all-cause mortality, nonfatal MI, or unstable angina requiring hospitalization, although the overall event rate was lower than expected. It should be noted, however, that although 70.1 % of patients randomized to CCTA were found to have enough coronary artery disease to justify protocol-directed aggressive medical management, only 5.7 % were found to have CAD severe enough to justify coronary revascularization through percutaneous coronary intervention (4.2 %) or coronary bypass graft surgery (1.5 %). Therefore, there was very limited power to assess the possible benefits of primary coronary revascularization.

Another recent study was the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE). This study randomly assigned 10,003 symptomatic patients with chest pain at low to moderate risk to a strategy of anatomical testing with CCTA, or to functional testing via exercise electrocardiography, nuclear stress testing, or stress echocardiography [23]. The goal of PROMISE was to determine if an initial non-invasive CCTA anatomic imaging strategy would improve clinical outcomes in subjects with CAD symptoms. This study demonstrated the improved diagnostic performance of CCTA over functional testing to detect obstructive disease. However, in this population of symptomatic patients with suspected CAD, CCTA did not improve clinical outcomes over a follow-up period of 2 years.

An earlier study by Hoffmann *et al.* (Rule Out Myocardial Ischemia/Infarction by Computer Assisted Tomography, ROMICAT-II) sought to determine whether an evaluation incorporating CCTA is more effective than standard evaluation done in the emergency department [24]. This study included 1000 patients with symptoms suggestive of acute coronary syndrome and had as its primary endpoint length of hospitalization stay. ROMICAT-II determined that incorporating CCTA improved the efficiency of clinical decision-making, compared to standard evaluation. However, it resulted in increased need for downstream tests and radiation exposure and did not show a decrease in the overall costs of care.

In this same 1000-patient population (from the ROMICAT-II

study), Truong *et al*. aimed to compare patients with and without diabetes to determine the differences in effectiveness and safety, downstream testing, and radiation exposure between the early CCTA and standard evaluation groups [25]. The primary endpoint, length of hospitalization stay, was not affected by the CCTA strategy for diabetic patients, although it was reduced for nondiabetic patients, compared with standard evaluation. CCTA did result in significant shortening of the emergency department stay of patients, suggesting that knowledge of coronary anatomy with CCTA may be beneficial for diabetic patients, and that with CCTA, one may determine the lower risk patients with no or little CAD who can be discharged immediately, as well as the higher risk patients with moderate to severe disease who warrant further work up.

To determine if screening and treatment of asymptomatic CAD are effective in preventing first cardiac events in patients with diabetes, the Does Coronary Atherosclerosis Deserve to be Diagnosed Early in Diabetic Patients? study (DADDY-D) enrolled 520 diabetic patients without known CAD who were randomly assigned to undergo screening for silent myocardial ischemia followed by revascularization or to continue follow up [26]. Again, in this study, only a small portion (4.6 %) of screened patients received protocol-driven coronary revascularization. In this diabetic sample, screening and revascularization of silent CAD failed to demonstrate a significant reduction in cardiac events and HF episodes. However, the data suggest that further research is warranted in patients older than 60 years and those with an intermediate cardiovascular risk.

To date, none of these published studies have demonstrated improvement in clinical outcomes with the use of CCTA screening, even if screening predicted future risk. Knowing that information, and even acting on it, did not appear to improve the outcomes of these high-risk patients. There are several potential reasons why no improvement in outcomes was detected:

1) As noted in FACTOR 64, if aggressive diabetic primary prevention therapy is implemented, including careful management of blood pressure, lipid, and glucose levels, these patients are no longer at high risk. It may therefore be difficult to improve clinical outcomes beyond the benefits afforded by optimal medical management. Thus, the lower event rate observed in FACTOR-64, and possibly in other studies, may be attributable to the optimal medical care received by the patients in these trials.
2) It is already recommended that patients with diabetes should receive aggressive medical therapy for secondary prevention. Hence, the only real way to change the management of these patients over what is recommended is to perform revascularization therapy. However, coronary revascularization may not always reduce future cardiac risk in asymptomatic patients. As pointed out earlier, this was tested in both COURAGE and the BARI 2D studies. Evidence and guidelines do exist that justify coronary revascularization for asymptomatic patients with severe three-vessel or left main coronary artery disease [27]. However, in the present trials, the numbers of patients identified with that degree of CAD severity was very small. Therefore, there is a potential need to find a more selective screening strategy to determine which asymptomatic patients might benefit from revascularization therapy. Preliminary screening for left ventricular systolic dysfunction or diffuse electrocardiographic abnormalities may help. Additionally, recent invasive functional coronary artery studies using pressure wires to measure the fractional flow reserve (FFR) have demonstrated a much-improved ability to predict the clinical utility of coronary revascularization [28, 29]. Although this invasive form of evaluation is not appropriate for asymptomatic screening, recent studies from Stanford University have proposed a non-invasive technique to determine FFR of selected coronary segments through sophisticated analysis of CCTR studies [30, 31]. However, even with more sensitive and specific screening modalities, with aggressive risk factor reduction, the numbers of asymptomatic diabetic patients who still may benefit from coronary revascularization may be too small to justify a general screening program.
3) Although coronary artery plaque severity may be associated with future CV risk, the potential for unstable plaque rupture may be a much more important predictor. Although CCTA may adequately show the presence of plaque [32], it has not yet demonstrated an ability to evaluate the vulnerability of that plaque. It may be advantageous to identify better screening methods that can determine risk of plaque rupture.

> The utility and value of screening for CAD in asymptomatic diabetic patients remain controversial.

Summary and conclusions

In summary, there is still no method of CAD screening identified that has been able to effectively reduce the cardiovascular risk of asymptomatic diabetic patients. Because of this fact, and as noted above, the most recent American Diabetic Association guidelines continue to recommend against screening for CAD in asymptomatic diabetic patients. However, even with presently known aggressive prevention therapy, diabetic patients still remain at substantial risk of adverse cardiovascular events. This calls for a continued search for better and more selective, sensitive, and specific screening methods, as well as more effective treatments, for this population.

The utility and value of screening for CAD in asymptomatic diabetic patients remain controversial. CCTA screening has shown promise and has been demonstrated to predict future risk, but as yet has not demonstrated improvement in the outcomes of these high-risk patients. Large randomized and well-controlled clinical trials must be done before any method for screening for CAD can be shown to reduce cardiovascular event rates in patients with diabetes.

Compliance with Ethical Standards

Conflict of Interest Joseph Brent Muhlestein and Fidela Ll. Moreno declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Arterial stiffness and increased cardiovascular risk in chronic kidney disease

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Cardiovascular disease (CVD) is a common comorbidity and a major cause of mortality in chronic kidney disease (CKD) patients. CVD-related mortality accounts for most deaths in young CKD adults. Recent studies have placed great emphasis on association of arterial stiffness (AS) and CVD. Increased AS is observed in young and even in pediatric CKD patients. Unparallel AS in young CKD patients and excessive risk of CVD in young CKD adults show an indication that AS probably offers one of the underlying mechanisms for linking CKD and CVD. The present paper summarizes the role of AS in CKD and CVD.

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Chronic kidney disease (CKD) is a global public health problem. Cardiovascular disease (CVD) is a common comorbidity and a major cause of mortality in CKD population. While CVD-related mortality is relatively uncommon in young population, it accounts for most deaths in young CKD adults. There are numerous risk factors for CVD in CKD patients including conventional (hypertension, diabetes, dyslipidemia) and nonconventional (oxidative stress, inflammation, anemia, mineral metabolism disorder) factors. Recent studies have placed great emphasis on the association of arterial stiffness (AS) and CVD. AS is traditionally known as an aging marker of the artery; however, increased AS is observed in young and even in pediatric CKD patients; it is also shown that AS progresses in consistent with kidney function decline. Unparallel AS in young CKD population and excessive risk of CVD in young CKD adults show an indication that AS probably offers one of the underlying mechanisms for linking CKD and CVD. AS in CKD patients has multifactorial causes. Comorbidities such as hypertension, diabetes, dyslipidemia, and mineral metabolism disorder which are risk factors for CVD also show great contribution to AS in CKD patients. Increased systolic blood pressure and decreased diastolic blood pressure resulting from AS cause elevated ventricular afterload, lead to impaired coronary perfusion, myocardial ischemia, and ventricular hypertrophy, and consequently develop into CVD event. In this review, we summarized the role of AS in CKD and CVD, aiming to explore the linkage of AS between CKD and CVD.

Introduction

Chronic kidney disease (CKD) is a global public health problem, affecting up to 16 % of the population [1–3]. It is believed that CKD is associated with increased risk of cardiovascular disease (CVD) [3, 4].

Cardiovascular disease has numeric risk factors. Besides those well-known traditional risk factors which include hypertension, diabetes, age and hyperlipidemia, arterial stiffness (AS) is accepted as an important nontraditional clinical predictor. Previous studies have showed that aortic stiffness is an independent risk factor for cardiovascular mortality [5], coronary heart disease, and fatal stroke [6]. Among different population including CKD, hypertension, diabetes, AS was found to be the strongest risk factor for CVD in end-stage renal disease (ESRD) patients [7, 8].

Increased AS is observed in early stages of CKD and accelerates with kidney function deterioration [9, 10]. Meanwhile, markers of increased aortic stiffness are shown to be powerful predictors of survival in ESRD patients [7, 8]. In addition, while AS is a hallmark of aging, it is found that AS exists in young CKD patients [11]. While CVD related mortality is relatively uncommon in young population, it still accounts for most deaths in young CKD adults [12]. CKD and AS have been identified as independent risk factors for CVD [13–17], and the unparalleled AS in young CKD population as well as the excessive risk of CVD in young CKD adults, all together indicates that AS probably offers one of the underlying mechanisms for linking CVD and CKD.

In this review, we would like to elaborate the association of CKD and CVD as well as the association of CKD and AS and try to elucidate the mechanism that AS might be involved in linking the increased CVD event in CKD population.

Increased CVD in CKD patients

Cardiovascular disease is the leading cause of morbidity and mortality worldwide; according to a report, about 3 million CVD deaths occur in both India and China annually [18]; in the USA, CVD mortality rate is 11.75 per 1000 person-years in general population [19]. However, CVD burden is even worse in patients with CKD [4, 20]. Studies showed that CKD patients had 3- to 30-fold higher risk of CVD, and CVD mortality was approximately 15 times higher in dialysis patients than in general population [21].

The high prevalence of CVD in ESRD patients indicates that CVD begins in earlier stages of CKD and increases consistently with kidney function deterioration.

A study also showed that the prevalence of coronary heart disease ranged from 4.5 to 24.5 % in CKD stage 3–5 patients, and when compared with estimated glomerular filtration rate (eGFR) >60 ml/min/1.73 m^2 cohort and adjusted for traditional confounders including prior CVD history, age, diabetes and hypertension, the CVD death risk is 3.4-fold higher in patients with eGFR <15 ml/min/1.73 m^2 [4]. Meanwhile, a Atherosclerosis Risk in Communities Study showed that the risk of CVD increased with 38 % in patients with baseline eGFR of 15–59 ml/ min/1.73 m^2 compared to those with baseline eGFR of 90–150 ml/min/1.73 m^2 [22]. It was also found that eGFR was independently associated with sudden cardiac death [23].

The high prevalence of CVD in ESRD patients indicates that CVD begins in earlier stages of CKD and increases consistently with kidney function deterioration [23, 24]. Even though the treatment for CVD has been improving dramatically over the past decades, CVD still takes responsibility for up to 50 % deaths in CKD population. Traditional risk factors including advanced age, diabetes, obesity, and lipid abnormalities contribute to the increased risk of CVD in CKD patients [19, 25, 26]. Besides, nontraditional risk factors which are more common in CKD population than in general population, including anemia, mineral and bone disorders, proteinuria, inflammation, and oxidative stress, also play roles in this excessive risk [26].

AS and CVD

In recent years, great emphasis has been placed on the role of AS in the development of CVD [27]; AS is accepted as an important nontraditional clinical predictor for CVD [28–31]. For AS assessment, central pulse wave velocity, measured as aortic pulse wave velocity (aPWV) or carotid–femoral pulse wave velocity (CFPWV), and central pulse pressure (CPP) are considered as current reference standard and the most robust measures for aortic wall stiffness. European Society of Cardiology and other societies demonstrated in the 2007 European guidelines that aPWV was an assessment of target organ damage [32, 33]. In the Framingham Heart Study, after adjustments for potential confounders, higher aPWV was found to be associated with a 48 % increase in CVD [29]. Prior studies emphasized the role of CFPWV and CPP as an independent cardiovascular risk factor and predictor of cardiovascular mortality not only in general population, but also in populations with coronary atherosclerosis, diabetes, ESRD, aging, coronary events, and stroke [14, 15, 30, 34–39]. A Japanese study showed that elevated brachial–ankle pulse wave velocity (baPWV) was a risk factor for re-admission or cardiac death of heart failure patients [30]. Meanwhile, a prospective observational study including 315 CKD stage 4–5 subjects demonstrated that aortic to femoral PWV was independently associated with cardiovascular outcome after a median follow-up of 3.6 years [34].

Several mechanisms can explain the pathophysiology of AS to cardiovascular event. It is believed that AS causes a premature return of reflected waves in late systole and, thus, increases central pulse pressure and systolic blood pressure (SBP), leading to increase in left ventricular (LV) afterload [27, 40]. Increase in the load on the left ventricle consequently leads to increase in myocardial oxygen demand, making the coronary perfusion/myocardial demand equilibrium unbalanced [41]. Additionally, increase in central pulse pressure and decrease in diastolic blood pressure (DBP) may directly cause subendocardial ischemia. Besides the impaired coronary perfusion, AS is associated with LV hypertrophy, which is a known risk factor for coronary events in normotensive and hypertensive patients [27]. The mechanisms are briefly illustrated in Fig. 1.

Association of AS and CKD

Arterial stiffness is recognized as an aging marker in general population; however, increased AS is observed in young CKD adults and even in pediatric CKD patients [11, 42]. Meanwhile, studies have also showed that AS progressed in consistent with decline in kidney function [9, 10, 43]. Cross-sectional studies indicated that there was a

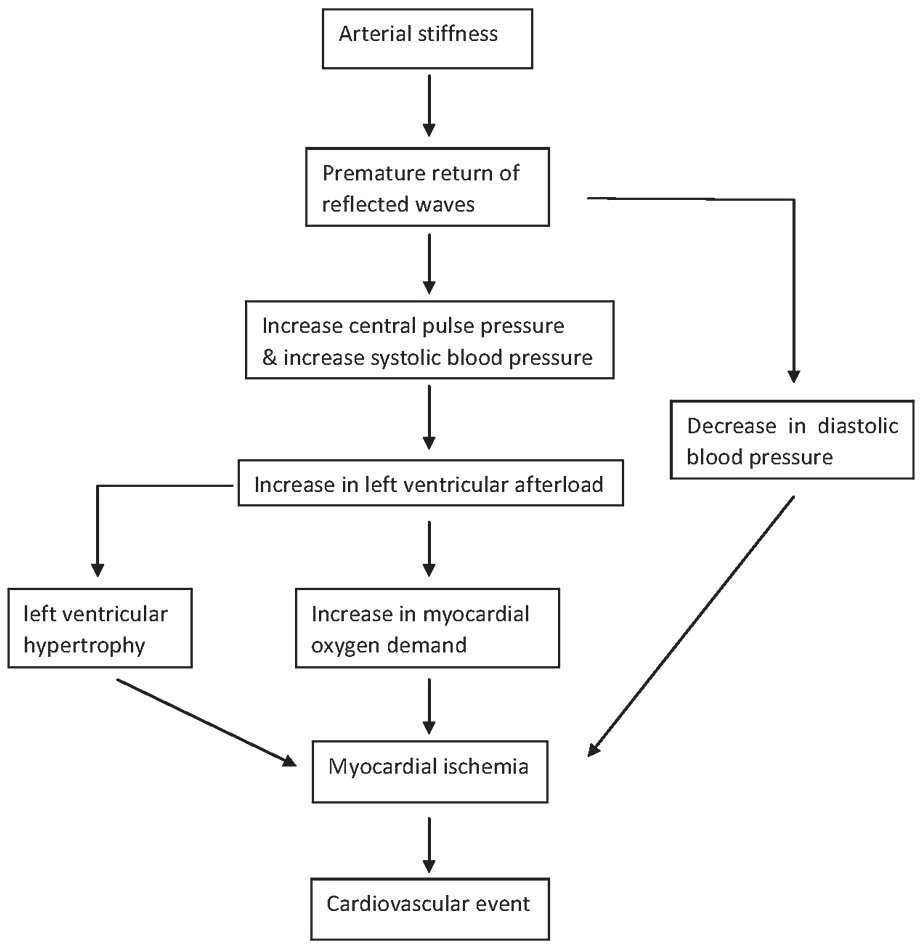

Fig. 1: Pathophysiology for arterial stiffness increases cardiovascular event.

Table 1. Studies on the association of arterial stiffness and chronic kidney disease.

References	Design	Population	Number
Peralta *et al.* [47]	Prospective	General old population (eGFR ≥60)	4853
Tomiyama [48]	Retrospective	Employees of a company	2053
Briet *et al.* [10]	Prospective	CKD	180
Madero *et al.* [45]	Prospective	General old population	2129
Nakagawa *et al.* [53]	Cross-sectional	CKD stage 1–5	647
Hermans *et al.* [49]	Cross-sectional	General old population	806
Townsend *et al.* [51]	Cross-sectional	Chronic renal insufficiency cohort	2564

negative association between AS and kidney function independent of blood pressure and other standard cardiovascular risk factors [9, 44]. This association exists not only in CKD cohorts but also in general population [9, 43, 45–52]. A Japanese study explored the relationship between eGFR and severity of AS in community using brachial–ankle pulse wave velocity (baPWV) as AS marker; the study found that there was a significant correlation between baPWV and eGFR after multiple regressions; furthermore, there was a stepwise increase in baPWV with CKD deterioration from stages 1–5 [53]. Moreover, a Chronic Renal Insufficiency Cohort Study with 2564 CKD participants showed that aortic PWV had a significant negative association with kidney function [51]. Despite the cross-sectional studies, longitudinal study yielded the similar results that increased AS occurred in parallel with the decline in kidney function in patients with mild-to-moderate CKD. A longitudinal study has captured an association between eGFR loss and AS even in individuals with normal GFR values [50]. In a Japanese occupational cohort with normal kidney function/early CKD, elevated AS was found to be an independent risk factor for the decline in kidney function [48]. A Korean study also showed that in patients with early stages of CKD, baPWV was independently associated with the decline in renal function and short-term cardiovascular events [54]. A Multi-Ethnic Study of Atherosclerosis Study with follow-up of 5 years showed that participants with eGFR ≥60 mL/min/1.73 m^2 were associated linearly and independently with faster kidney function decline [47]. A meta-analysis consisted of 15,877 subjects and followed up for a mean of 7.7 years showed the same results that eGFR was significantly associated with AS, independent of traditional risk factors for CVD [55]. Recently, a study showed that baseline baPWV was independently associated with a rapid decline in eGFR in diabetes patients [56]. Also, a study revealed that aortic stiffening is independently associated with rate of change in kidney function in patients with CKD stages 3 and 4 [46]. Studies showing the association of AS and CKD in recent years are summarized in Table 1.

Chronic kidney disease is characterized by a high prevalence of conventional (hypertension, diabetes, dyslipidemia) and nonconventional (oxidative stress, inflammation, anemia, mineral metabolism disorder) cardiovascular risk factors [57–60], and long-term exposure to this environment might induce remodeling and stiffening in arterial structure. Arterial stiffening in renal disease involves several mechanisms. One hypothesis is that decline in kidney function is associated with endothelial dysfunction which will lead to atherosclerosis. Moreover, oxidative stress, inflammation, uremic toxins, and dyslipidemia play a role in endothelial dysfunction, vascular calcification, and vascular smooth muscle hypertrophy which potentially lead to collagen deposition and influence medial thickening, calcification and fibrosis [42, 61]. Meanwhile, the disturbed mineral metabolism in CKD patients will exacerbate the vascular calcification and trigger transformation of vascular smooth muscle cells into a synthetic phenotype, depositing collagen I- and collagen III-rich extracellular matrix in the arterial wall, thus leading to AS (Fig. 2) [42, 62].

AS in the development of CVD event in CKD patients

Arterial stiffness as an independent cardiovascular risk factor and predictor of cardiovascular mortality is found not only in general population and patients with heart disease, but also in CKD patients [11, 34]. Among different population including CKD, hypertension, diabetes, AS was found to be the strongest risk factor for CVD in ESRD patients [7, 8].

According to prior studies, increased AS has been associated with kidney impairment and progression of CKD [63–65]. Aortic stiffness is known as decreased elasticity, decreased compliance, and increased wall thickness in vessels, which potentially

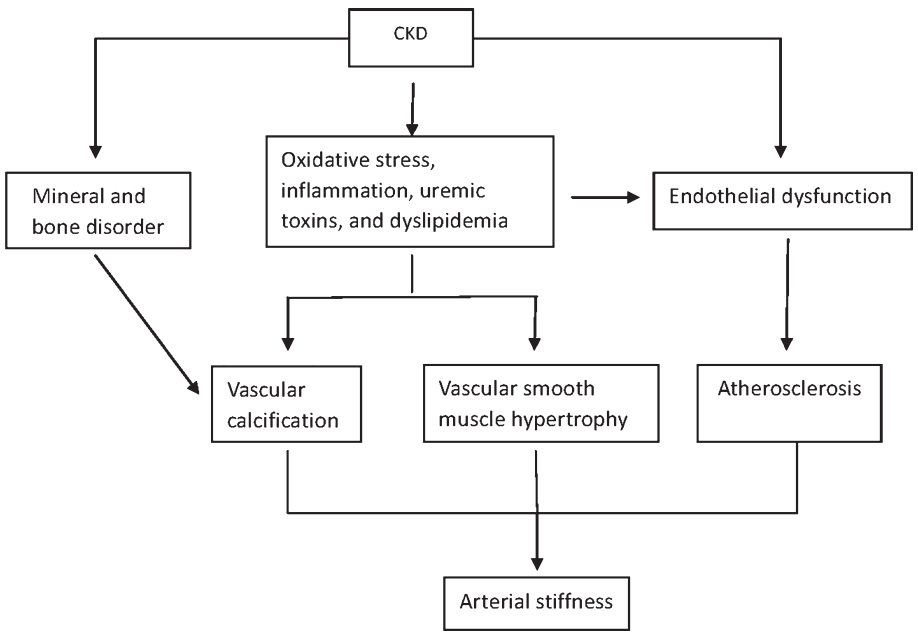

Fig. 2: Mechanism of arterial stiffening in chronic kidney disease.

Table 2. Studies on the treatment strategies of central arterial stiffness.

References	Design	Treatments	Main findings
ARB/ACEI			
Peng *et al.* [74]	Meta-analysis	ARB	Reduced CFPWV
Shahin *et al.* [75]	Meta-analysis	ACEIs	Reduce PWV
Tsang *et al.* [73]	RCT	Quinapril	Reduced arterial stiffness
Peng *et al.* [74]	Meta-analysis	CCB	Reduced CFPWV

CCB calcium channel blocker, *RCT* randomized clinical trial.

cause hemodynamic changes. The kidney is a high-flow and low-impedance organ; thus, it is vulnerable to hemodynamic changes in the central vasculature. A logical pathophysiological explanation for kidney impairment can be offered that torrential flow and low resistance to flow in kidney expose small arterial vessels to the high-pressure fluctuations, which is measurable as central pulse pressure. Exposure of small vessels to highly pulsatile pressure and flow accounts for the microvascular damage and sequentially results in renal insufficiency. It is showed that damage of large arteries is the major contributory factor to the high cardiovascular morbidity and mortality in ESRD patients [63–65]. Studies implicated that macro-vascular disease developed rapidly in uremic patients was responsible for occurrence of ischemic heart disease, LV hypertrophy, congestive heart failure, sudden death, and stroke [63]. When atherosclerosis is considered as the major arterial changes in traditional heart disease, many arterial complications in ESRD patients arise without the presence of atherosclerosis; instead, arterial stiffening is responsible for the principal arterial alterations and is associated with arterial enlargement and hypertrophy [66]. The stiffening of the artery in CKD and ESRD patients is believed to be associated with the alterations in the intrinsic elastic properties of arterial walls [42, 67], and these arterial wall changes are associated with uremia status per se. Meanwhile, mineral and bone disorders due to CKD and ESRD also play significant roles in arterial remodeling and functional alterations [68, 69]. In hemodialysis patients, AS was associated with arterial calcifications [69, 70], which is a well-known risk factor for CVD, and AS worsened with increasing calcifications [71].

Arterial stiffness causes a premature return of reflected waves in late systole and sequentially leads to increased central pulse pressure, elevated SBP, and decreased DBP and higher pulse pressure. As is well identified, elevated SBP and pulse pressure, lower DBP are independent factors of cardiovascular morbidity and mortality in general population as well as in ESRD patients [71]. High SBP and low DBP cause increase in afterload in left ventricle and decrease in coronary perfusion [72], thus leading to LV hypertrophy, coronary ischemia, damage of arterial wall tissues, and potentially results in myocardial ischemia, heart failure, and sudden death. Furthermore, high blood pressure contributes to acceleration of aortic stiffness. It has been shown that elevated blood pressure, especially increased pulse pressure, increases pulsatile aortic wall stress, which accelerates elastin degradation. Thus, hypertension is viewed as an accelerated form of vascular aging that leads to aortic stiffening. From this pathway, AS corresponds to the excessive CVD risk in CKD, and it plays an important role as a linkage between the CKD and CVD.

Treatment strategies of central arterial stiffness

The contribution of AS to the pathogenesis of hypertension and the role of hypertension in causing AS has important clinical implications in the treatment of AS. Drugs currently approved to be effective for treating hypertension were explored whether they could substantially reduce AS. Angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARB), low-dose diuretics, calcium channel antagonists, and some beta-blockers have been proved to have favorable effects on arterial stiffness (Table 2) [73, 74–75]. In high-risk patients with end-stage renal failure, ACE inhibitors effectively decreased arterial stiffness and had a favorable effect on survival which was independent of changes in blood pressure [73]. A recent meta-analysis including qualified clinical trials and 1650 and 1659 subjects in ARB treatment and control groups has supported an important role of ARB treatment in improving arterial stiffness [74]. Another meta-analysis summarizing five randomized controlled trials has observed that ACEIs reduce PWV; however, it is not clear whether ACEIs are superior to other antihypertensive agents in their effect on AS [75]. Treatment strategies need further evaluation on which agent is superior to the others or if combination use of the agents gain more benefit than single agent in treatment of AS patients.

Conclusions and perspectives

In clinic, prevention and treatment of CVD are major considerations in the management of CKD. Studies postulated that the AS is associated with CVD and CKD, and the unparallel AS and CVD and the excessive risk of CVD in CKD patients indicate that AS contributes to the development of CVD in CKD. The mechanism involving in the pathophysiology implicates that AS might be

Cont'd on page 29..

The importance of proteinuria and prior cardiovascular disease in all major clinical outcomes of atherosclerotic renovascular disease – a single-center observational study

Identification of patients at risk of developing adverse events would enable aggressive medical therapy and possibly targeted revascularization. The aim of this study is to characterize the determinants of long-term outcomes in atherosclerotic renovascular disease (ARVD). Patients with a radiological diagnosis of ARVD were recruited into this single-center prospective cohort study between 1986 and 2014. Data collected included baseline co-morbid conditions, annualized prescribed medications and laboratory data (serum creatinine [υmol/L], proteinuria [g/24 h]). Multivariable Cox regression analysis was used to explore association with these end-points: death, end-stage kidney disease (ESKD), cardiovascular event (CVE) and the first of any of these events. A total of 872 patients were recruited into this study. However, 42 patients were excluded due to missing baseline data and hence case records for 830 patients were reviewed. Over median follow-up of 57.1 months (interquartile range: 21.7–96.9), incidence per 100 patient years of death, ESKD, CVE and any event was 13.5, 4.2, 8.9 and 21.0 respectively. Macrovascular disease (MVD), congestive heart failure (CHF), flash pulmonary oedema (FPE) and greater proteinuria at baseline were individually associated with increased risk for all end-points in multivariable analysis (Death: MVD –HR 1.24 [95 % CI 1.02–1.50]; CHF –HR 1.33 [95 % CI 1.08–1.64]; FPE – HR 2.10 [95 % CI 1.50–2.92]; proteinuria – HR 1. 14 [95 % CI 1.08–1.20]). Higher estimated glomerular filtration rate at time of diagnosis was significantly associated with reduced risk of all end-points (Death: HR 0.92 [95 % CI 0.89–0.94]). Administration of statins and renin angiotensin blockade (RAB) at baseline were also associated with reduced adverse events, especially death (RAB: HR 0.83 [95 % CI 0. 70–0.98]; statins: HR 0.79 [95 % CI 0.66–.94]) and ESKD (RAB: HR 0.84 [95 % CI 0.71–1.00]; statins: HR 0.79 [95 % CI 0.66–0. 93]). Revascularization was associated with reduced risk of death (HR 0.65 [95 % CI 0.51–0.83]) and ESKD (HR 0.59 [95 % CI 0.46–0.76]). All patients with ARVD require intensive vascular protection therapy to help mitigate systemic atherosclerosis, optimize cardiovascular risk and improve clinical outcomes. More effort is required to identify the minority of patients who may benefit from revascularization.

References available on request
Healthcare.India@springer.com

Source: Diana Vassallo, James Ritchie, Darren Green. The importance of proteinuria and prior cardiovascular disease in all major clinical outcomes of atherosclerotic renovascular disease – a single-center observational study. BMC Nephrol 2016;17:198. DOI 10.1186/s12882-016-0409-1.

Threshold and target for blood pressure lowering in the elderly

Detection of elevated blood pressure values in elderly patients represents a common clinical condition associated with an increased cardiovascular risk. This has been shown to be the case in both systodiastolic and isolated systolic hypertension as well. However, despite the evidence of the benefits of the blood pressure lowering intervention in terms of reduction of cardiovascular morbidity and mortality, at least two issues related to antihypertensive drug treatment in aged individuals are still undefined: (1) the blood pressure threshold at which antihypertensive drug should be initiated and (2) the blood pressure goals of the therapeutic intervention. The present paper will critically review the evidence available so far on these two issues as well as the position of current guidelines and consensus statements. Emphasis will be given to the analysis of the new data of the Systolic Blood Pressure Interventional Trial (SPRINT), which have recently demonstrated the benefits, even in individuals aged more than 75 years, of a tight blood pressure reduction to systolic blood pressure to 120 mmHg or less. The potential limitations of the trial will be also critically addressed and the expectations of ongoing clinical studies investigating the issue in elderly patients properly emphasized. Although of interest, the results of the SPRINT trial encompass a number of limitations which limit their applicability to the general elderly hypertensive population. A prudent approach will be to adopt in clinical practice the less intensive and more conservative targets recommended by current guidelines.

References available on request
Healthcare.India@springer.com

Source: Guido Grassi, Fosca Quarti-Trevano, Anna Casati. Threshold and target for blood pressure lowering in the elderly. Curr Atheroscler Rep. 2016;18: 70. DOI 10.1007/s11883-016-0627-9.

Global cardiovascular risk assessment: strengths and limitations

Global cardiovascular (CV) risk assessment tries to answer the questions: who will benefit from intervention? And when should non-pharmacologic and pharmacologic treatment be started? Used for the assessment of CV risk in the presence of one main CV risk factor, the presence of previous CV disease, diabetes, chronic kidney disease, coronary heart disease and severely elevated single risk factors, are situations with a high or very high risk. For the majority of subjects without any of the above, a calculation of risk can help to decide the best management. The methodology of assessing global CV risk has both strength and limitations. Several computational methods have been developed to assess global CV risk but no risk estimation can consider all the potential risk factors. The most used score chart is the Framingham CardioVascular Risk Score, although in Europe the Systematic Coronary risk evaluation is widespread. The strengths of the global CV risk scores depend on the methodology applied at the time of construction: (a) appropriate statistical methods (representative sample, sufficient power, clear definition of the outcomes); (b) inclusion of appropriate risk factors (age, sex, conventional risk factors, and inclusion of others that can be relevant). Once developed, the function requires internal and external validity as well as calibration. There ware several limitations, which have been solved with different approaches. In the case of hypertension, one element is introduced in the score charts, the presence of hypertension-induced organ damage offering a refinement of the approach to the global CV risk.

References available on request
Healthcare.India@springer.com

Source: Diana Vassallo, James Ritchie, Darren Green. The importance of proteinuria and prior cardiovascular disease in all major clinical outcomes of atherosclerotic renovascular disease – a single-center observational study. BMC Nephrol. 2016;17:198. DOI 10.1186/s12882-016-0409-1.

Effects of a change over from other angiotensin II receptor blockers to olmesartan on left ventricular hypertrophy in heart failure patients

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Since olmesartan increases plasma angiotensin-(1–7) through an increase in angiotensin-converting enzyme-related carboxypeptidase (ACE2) expression, it was hypothesized to reduce LVH, unlike other angiotensin II receptor blockers (ARBs). The objective of this study was therefore to investigate the effects of a changeover from other ARBs to olmesartan on left ventricular hypertrophy in heart failure patients.

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Left ventricular (LV) hypertrophy (LVH) is an independent cardiovascular risk factor for heart failure (HF) patients. The renin–angiotensin system plays a key role in LVH, and since olmesartan increases plasma angiotensin-(1–7) through an increase in angiotensin-converting enzyme-related carboxypeptidase (ACE2) expression, it was hypothesized to reduce LVH, unlike other angiotensin II receptor blockers (ARBs). The objective of this study was therefore to investigate the effects of a changeover from other ARBs to olmesartan on LVH in HF patients. Participants enrolled in this prospective trial were 64 outpatients with stable HF who had received ARBs other than olmesartan for more than 1 year (age: 59 ± 13 years). Transthoracic echocardiography and laboratory tests were performed before and 6 months after administration of olmesartan. Other drugs were not changed during followup. The primary end point was defined as a change in LV mass index (LVMI) from baseline up to 6 months after administration of olmesartan. No significant changes were observed in blood pressures and heart rate after administration of olmesartan. LVMI showed a significant decrease from 119 ± 38 to 110 ± 24 g/m^2 ($p = 0.007$) 6 months after administration of olmesartan, and further decreased from 110 ± 24 to 103 ± 35 g/m^2 ($p = 0.0003$) after 12 months. Moreover, this reduction tended to be more prominent in patients with LVH. In conclusions, LVH in HF patients was reduced by the changeover to olmesartan. This finding may well have clinical implications for better management of HF patients.

Introduction

Left ventricular (LV) hypertrophy (LVH) is an independent cardiovascular risk factor in the general population, and occurs in various types of heart failure (HF) patients such as those with HF with reduced ejection fraction (EF) (HFrEF) and HF with preserved EF (HFpEF) [1–3]. Since the development of LVH was found to be associated with progression to HF, interest has been high in treatment to reduce LVH in HF patients. A meta-analysis of the effects of treatment on LV mass in essential hypertension reported that angiotensin (Ang) II receptor blockers (ARBs), angiotensin- converting enzyme (ACE) inhibitors, and calcium channel blockers reduced LV mass by approximately 10–13 % [4]. ARBs are widely used in the treatment of hypertension, and large-scale clinical studies have shown that they have a variety of effects, not only their anti-hypertensive effect but also prevention of the progression of HF [5]. The renin–angiotensin system (RAS) plays a key role in LVH, and Ang II is a major determinant in this process [6]. Ang II stimulates LVH and fibrosis in HF patients, whereas Ang II blockade prevents development of LVH [7–10]. An ACE-related carboxypeptidase, known as ACE 2, was identified in the human heart, and ACE 2 degrades Ang I into Ang-(1–9) and Ang II into Ang-(1–7) [11–13]. Characterization of the actions of Ang-(1–7) has demonstrated that the RAS consists of an important biochemical arm which generates Ang II via the action of ACE on Ang I. In addition, the RAS possesses another important biochemical arm which generates Ang-(1–7) from either Ang I or Ang II via enzymes other than ACE [14, 15]. The discovery of ACE 2 and the demonstration that its catalytic efficiency is approximately 400-fold higher with Ang II as a substrate than with Ang I [16], as well as the report that the ARB olmesartan is associated with high activity of ACE2 and increases Ang-(1–7) via ACE2 [17–21], suggest that olmesartan may have the capability to reduce LVH in HF patients more than other ARBs.

Findings of recent reports suggest that olmesartan may have the capability to reduce LVH in HF patients more than other ARBs.

The objective of this study was, therefore, to investigate the effects on LVH in HF patients of a changeover from other ARBs to olmesartan.

Methods

Study population

Participants enrolled in this prospective trial were 64 outpatients with stable HF who had been treated with ARBs other than olmesartan for more than 1 year at Kobe University Hospital between December 2013 and March 2016. We excluded patients with (1) the development of HF within 3 months; (2) hypotension <90/50 mmHg; (3) severe types of renal dysfunction defined as serum creatinine level (Cr) >3 mg/dl; (4) atrial fibrillation; and (5) administration of ACE inhibitors. At the time of enrollment, all patients were in clinically stable condition. The trial was registered with the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (registration number UMIN000011807), conformed to the principles outlined in the Declaration of Helsinki, and was performed with the approval of the Ethics Committee of Kobe University Hospital. Written informed consent was obtained from all patients.

Study protocol

Patients who had consented to their participation in this study switched from other ARBs to olmesartan on the basis of the findings of their most recent late phase II dose-finding studies to maintain blood pressure [22–26] (Table 1). Other drugs were not changed after the change to olmesartan. The physical examinations, blood tests, and echocardiography were performed on the same day at baseline and 6 months after administration of olmesartan. Blood pressure was measured after at least 15 min of rest in a supine position and before echocardiography by a physician (H.S.), and was determined by averaging two consecutive measurements (Terumo Elemano Blood Pressure Monitor; Terumo, Tokyo, Japan).

Table 1. The other ARBs-to-olmesartan conversion table.

Other ARBs dose (mg/day)					Olmesartan dose (mg/day)
Losartan	Candesartan	Valsartan	Telmisartan	Azilsartan	
25	4	40	20	10	5
50	8	80	40	20	10
100	16	160	80	40	20

ARB angiotensin II receptor blocker.

Echocardiographic examination

Two-dimensional echocardiography was performed using a commercially available ultrasound system (Aplio Artida; Toshiba Medical Systems, Tochigi, Japan). Digital routine grayscale two-dimensional cine loops from three consecutive heartbeats were obtained at end-expiratory apnea from the standard parasternal views and three apical views. Sector width was optimized to allow for complete myocardial visualization while maximizing the frame rate. LV measurements were obtained in accordance with the current guidelines of the American Society of Echocardiography/ European Association of Cardiovascular Imaging [27]. The early diastolic (E) and atrial wave velocities (A) and the E-wave deceleration time were measured using the pulsed wave Doppler recording from the apical four-chamber view. Spectral pulsed-wave Doppler-derived early diastolic velocity (e') was obtained from the septal mitral annulus, and the E/e' ratio was calculated to obtain an estimate of LV filling pressure [28]. LV mass was estimated from the formula proposed by Devereux *et al*., and LV mass index (LVMI) was calculated for each subject by dividing LV mass by body surface area [29]. LVH was defined as LVMI >95 g/m^2 for females and >115 g/m^2 for males [27].

Definitions of end point

The primary end point was defined as a change in LVMI between baseline and 6 months after the start of administration of olmesartan. The secondary end points comprised a change in brain natriuretic peptide (BNP), E/A, e' and E/e' between baseline and 6 months after the start of administration of olmesartan.

Statistical analysis

Continuous variables were expressed as mean ± SD or percentages, while categorical data were summarized as frequencies

and percentages. The parameters of the two subgroups were compared by means of Student's t test or Wilcoxon rank sum test as appropriate. Assuming 30 % of patients with decreased LVMI 6 months after administration of olmesartan, an alpha error of 0.05, a beta error of 0.2, and statistical power of 80 %, and the sample size requirement was 44 patients. However, considering a potential 25 % dropout or loss to follow up rate, 58 will be considered. Statistical significance was basically defined as p value <0.05 for each step. MedCalc version 15.11.4 (MedCalc Software, Mariakerke, Belgium) was used for all analyses.

Results

Three initially eligible patients (4.7 %) were excluded from all subsequent analyses because of lost follow-up, so that the final study group consisted of 61 patients. There were no cardiac events or deaths during follow-up. The baseline clinical and echocardiographic characteristics of the 61 HF patients are summarized in Tables 2 and 3. Their mean age was 59 ± 13 years, LVEF was 46 ± 12 %, and 24 patients (39 %) were female. HFpEF was observed in 23 patients (38 %), and the remaining 38 patients (62 %) were classified as HFrEF. No significant changes were observed in systolic and diastolic blood pressures and heart rate 6 months after administration of olmesartan (120 ± 20 vs. 121 ± 21 mmHg, p = 0.9; 70 ± 11 vs. 72 ± 13 mmHg, p = 0.9; 67 ± 11 vs. 67 ± 12 bpm, p = 0.86, respectively, Table 3).

Primary end point

LVMI showed significant decreases from 119 ± 38 to 110 ± 24 g/m^2 (p = 0.007) 6 months after administration of olmesartan (Fig. 1). In addition, LVMI showed significantly further decreased from 110 ± 24 to 103 ± 35 g/m^2 (p = 0.0003) of 51 patients 12 months after administration of olmesartan available (Fig. 1). Patients with LVH, defined as an LVMI >95 g/m^2 for female and >115 g/m^2 for male, were observed in 34 patients (56 %), and the remaining 27 patients (44 %) were classified as without LVH (Fig. 2). Reduction of LVMI for patients with LVH was significantly higher than that for patients without LVH both between baseline and 6 months after the start of administration of olmesartan (−24.1 ± 29.3 vs. 1.6 ± 26.9 g/m^2, p < 0.001), and between baseline and 12 months after the start of administration of olmesartan (−41.0 ± 44.0 vs. -5.7± 23.3 g/m^2, p < 0.001).

Secondary end point

The results of using the secondary end point are shown in Fig. 3. BNP tended to decrease 6 months after the start of administration of olmesartan from 52 pg/mL (17–182) to 40 pg/mL (19–129) (p = 0.2), but the difference was not statistically significant. No significant changes were observed in *E/A*, *e′* and *E/e′* 6 months after administration of olmesartan.

Other echocardiographic parameters

Other echocardiographic parameters, such as LV end-diastolic diameter, intra-ventricular septal thickness, and LV end-diastolic and end-systolic volumes, were also significantly reduced 6 months after the start of administration of olmesartan (Table 3).

Discussion

The findings of our study indicate that LVMI for HF patients, who had received other ARBs, significantly decreased 6 months after the changeover to olmesartan despite similar blood pressures and further decreased after 12 months. This reduction tended to be more prominent in patients with LVH. This is the first study to demonstrate the further

Table 2. Baseline characteristics of the patients.

Age, years	59 ± 13
Gender (female), n (%)	24 (39)
Body surface area, m^2	1.67 ± 0.21
Medications, n (%)	
Diuretics	21 (35)
β-Blockers	54 (89)
Spironolactone	24 (39)
Calcium channel blockers	7 (11)
ARBs, n (%)	61 (100)
Losartan	21 (35)
Candesartan	24 (39)
Valsartan	11 (18)
Telmisartan	2 (3)
Azilsartan	3 (5)
Etiology of heart failure, n (%)	
HFpEF	23 (38)
EFrEF	38 (62)
Dilated cardiomyopathy	24 (39)
Cardiac sarcoidosis	7 (11)
Valvular heart disease	4 (7)
Ischemic cardiomyopathy	2 (3)
Cardiac amyloidosis	1 (2)

ARB angiotensin II receptor blocker, *HFpEF* heart failure with preserved ejection fraction, *HFrEF* heart failure with reduced ejection fraction.

Table 3. Changes of after administration of olmesartan.

	Baseline	6 months after administration of olmesartan	p value
Systolic blood pressure, mmHg	120 ± 20	121 ± 21	0.9
Diastolic blood pressure, mmHg	70 ± 11	72 ± 13	0.9
Heart rate, bpm	67 ± 11	67 ± 12	0.9
BNP, pg/mL	52, 17–182	40, 19–129	0.2
Echocardiographic parameters			
LV end-diastolic diameter, mm	54 ± 8	52 ± 8	<0.01
LV end-systolic diameter, mm	42 ± 11	41 ± 11	0.1
Intra-ventricular septal thickness, mm	9.8 ± 3.1	9.4 ± 2.6	0.02
LV posterior wall thickness, mm	9.5 ± 2.2	9.8 ± 1.8	0.4
LV end-diastolic volume, mL	124 ± 49	113 ± 39	<0.01
LV end-systolic volume, mL	72 ± 44	65 ± 35	<0.01
LV ejection fraction, %	46 ± 12	45 ± 11	0.8
Left arterial volume index, mL/m^2	40 ± 22	39 ± 20	0.6
Early diastolic wave velocity, cm/s	61 ± 22	61 ± 23	0.9
Arterial wave velocity, cm/s	65 ± 18	67 ± 18	0.4
E/A	0.99 ± 0.54	0.95 ± 0.57	0.6
e′, cm/s	6.0 ± 2.4	5.7 ± 2.1	0.1
E/e′	11.6 ± 7.0	11.4 ± 6.66	0.9
LV mass index, g/m^2	119 ± 38	110 ± 24	0.007

LV left ventricular, *E/A* early diastolic and atrial wave velocities ratio, *e′* early diastolic septal mitral annulus velocity, *E/e′* early diastolic and mitral annulus velocities ratio, *BNP* brain natriuretic peptide.

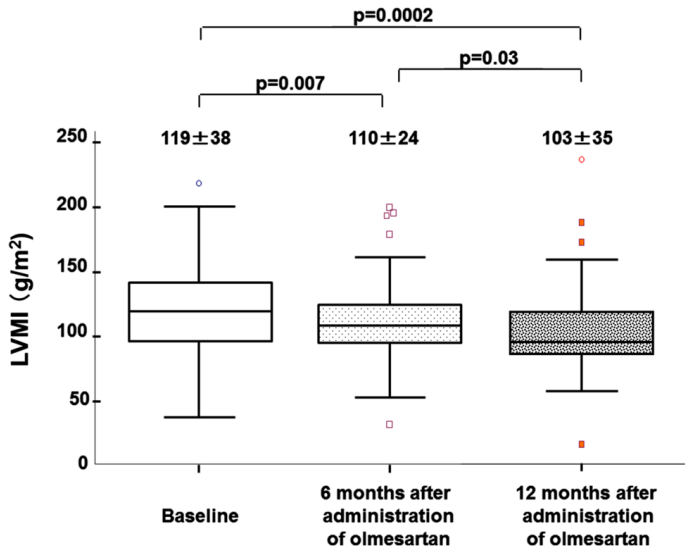


Fig. 1: Primary end point. Left ventricular mass index (LVMI) showed significant reductions 6 months after the start of administration of olmesartan, and had further decreased significantly 12 months after administration of olmesartan.

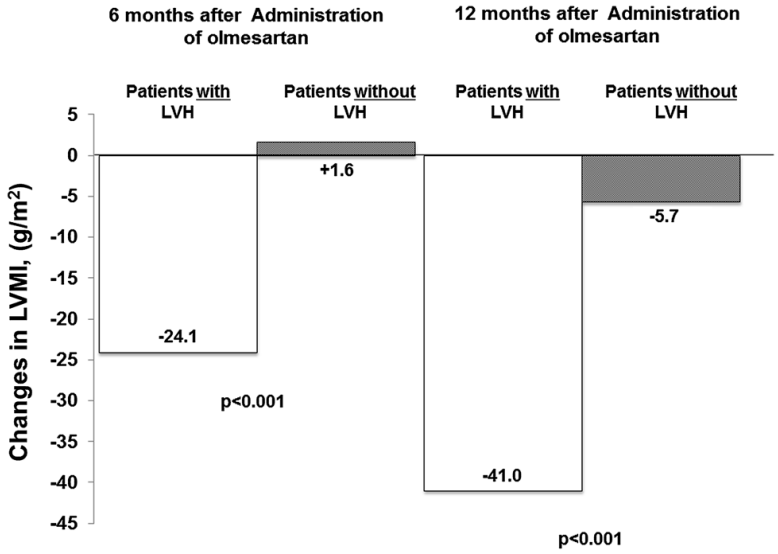


Fig. 2: Reduction in left ventricular mass index (LVMI) for patients with left ventricular hypertrophy (LVH) was significantly higher than that for patients without LVH both between baseline and 6 months after the start of administration of olmesartan, as well as between baseline and 12 months after the start of administration of olmesartan.

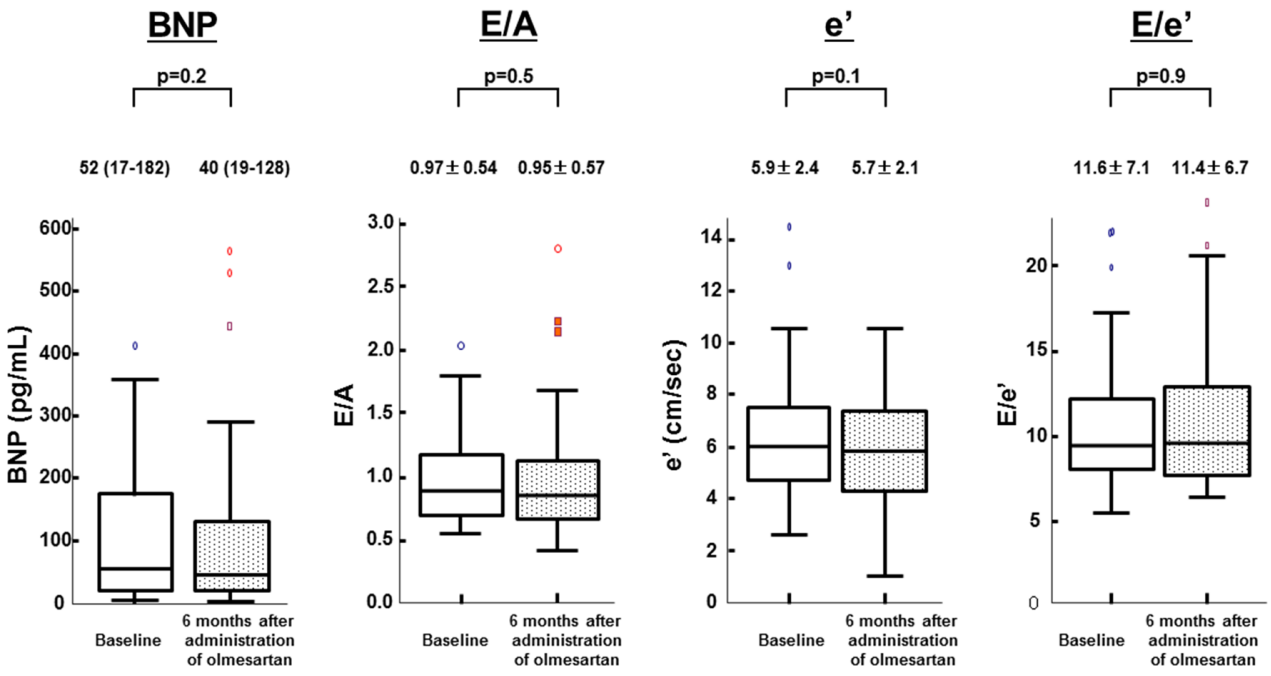


Fig. 3: Secondary end point. Brain natriuretic peptide (BNP) tended to decrease 6 months after the start of administration of olmesartan, but the difference was not statistically significant. No significant changes were observed either in *E/A, e'* and *E/e'* at the same point in time.

reduction in LVH attainable with olmesartan as compared with that attained with ARBs.

Effect of olmesartan on of LV hypertrophy reduction

LVH is an independent cardiovascular risk factor in the general population and occurs in various types of HF patients [1–3]. The development of LVH has been associated with progression to HF as characterized by increased LV end-diastolic pressure and diminished LV contractility. A meta-analysis of the effects of treatment on LV mass in essential hypertension reported that ARBs, ACE inhibitors, and calcium channel blockers reduced LV mass by approximately 10–13 % [4]. The RAS plays a key role in LVH, and Ang II is a major determinant in this process [6]. Ang II stimulates LVH and fibrosis in HF patients, whereas Ang II blockade prevents development of LVH [7, 8]. Moreover, Ang II also causes LVH independent of its effect on blood pressure, whereas blockade of the RAS attenuates or reverses the cellular adaptations to pressure overload [30, 31]. An ACE-related carboxypeptidase, known as ACE 2 and identified in the human heart degrades Ang I into Ang- (1–9) and Ang II into Ang-(1–7) [11–13]. Characterization of the actions of Ang-(1–7) demonstrated that the RAS consists of two biochemical arms: one generates Ang II via the action of ACE on Ang I, and the second generates Ang-(1–7) from either Ang I or Ang II via enzymes other than ACE [14, 15]. The discovery of ACE 2 was followed by the demonstration that its catalytic efficiency is approximately 400-fold higher with Ang II as a substrate than with Ang I [16]. In this study, we showed that olmesartan may have the potential to exert a stronger reductive effect on LVH than any other ARBs. The reason for this is that olmesartan features a higher activity of ACE2 than other ARBs, and increases Ang-(1–7) via ACE2 more than do the other ARBs [17–21]. Several previous investigators have reported that

the use of olmesartan was advantageous for attaining regression of LVH. Agata *et al*. reported that the long-term administration of olmesartan in an animal study caused an increase in renin activity, no changes in angiotensin II, and a decrease in aldosterone [32]. This resulted in reductions in LVMI, coronary arterial wall lumen ratio and perivascular fibrosis, as well as improvement in cardiovascular remodeling. Igase *et al*. reported that olmesartan reduced the thickness of the tunica media of the abdominal aorta and that this led to an increase in Ang-(1–7) [33]. Yokoyama *et al*. found that olmesartan showed definite inhibitory effects on LVH and mesenteric arterial hypertrophy, and that these effects on cardiovascular remodeling were due to factors related to hypotensive effects and also factors not dependent on blood pressure [34].

It has been suggested that the aldosterone breakthrough is an important risk factor for cardiovascular disease progression including the progression of LVH, despite the use of ACE inhibitors or ARBs [35–37]. Sezai *et al*. evaluated the effects of a changeover from candesartan to olmesartan on the renin–angiotensin–aldosterone system in 56 patients with essential hypertension found that angiotensin II and aldosterone are reduced by a changeover from candesartan to olmesartan. Furthermore, LVMI and BNP decreased 6 months and 12 months after the changeover [38]. In another clinical study which compared the effects of candesartan and olmesartan [39], Tsutamoto *et al*. found no difference between the effects of the two drugs on aldosterone, but Ang II was significantly lower for the group after 3 months to one year of olmesartan administration. The rate of reduction in the LVMI of the olmesartan group was significantly higher after 1 year of administration, and the rates for Ang II and LVMI reduction correlated [39]. Thus, olmesartan may be associated with a lower incidence of aldosterone breakthrough than attainable with other ARBs, so that this may be one of the reasons for the more pronounced regression of LVH.

Clinical implications

As mentioned before, LVH is an independent cardiovascular risk factor for various types of HF patients. The use of ARBs has been highly recommended for HF patients, especially those with HFrEF [5]. On the other hand, there is no established pharmacological treatment for a better prognosis of patients with HFpEF. LVH was found to be present in the majority of patients with HFpEF, and LV mass to be independently associated with an increased risk of morbidity and mortality [40]. Our findings indicate that the use of olmesartan rather than other ARBs may lead to regression of LVH, and may result in a favorable clinical outcome for patients with HFrEF and HFpEF.

Study limitations

There were certain limitations to this study. First, ACE2 and Ang-(1–7) were not measured in this study, so that we were not sure that LVH was determined by ACE2 and Ang-(1–7) to a greater than other factors such as hemodynamics. Second, the assessment of cardiopulmonary test, and cardiothoracic ratio in chest X-ray, and 12-lead electrocardiogram to evaluate the effects of a changeover from other ARBs to olmesartan was not part of this study. Finally, we used only echocardiography to assess LVH, and the assessment of LVH by means of cardiac magnetic resonance imaging was not part of this study.

Our findings indicate that the use of olmesartan rather than other ARBs may lead to regression of LVH, and may result in a favorable clinical outcome for patients with HFrEF and HFpEF.

Conclusions

LVH of HF patients was reduced following the changeover from treatment with other ARBs to that with olmesartan. This finding may well have clinical implications for better management of HF patients. This study covered a small number of patients in a single-center study, so that the future prospective studies of larger patient populations with randomly assigned to receive olmesartan or other ARBs or crossover study are necessary to validate our findings.

Acknowledgments The authors are grateful for the support of the entire staff of the echocardiography laboratories of the Kobe University Hospital.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

References available on request Healthcare.India@springer.com

Source: Hiroyuki Shimoura, Hidekazu Tanaka, Kensuke Matsumoto, et al. Effects of a changeover from other angiotensin II receptor blockers to olmesartan on left ventricular hypertrophy in heart failure patients. Heart Vessels. 2017; Advance online publication. DOI 10.1007/s00380-016-0904-0.

Cont'd from page 23

an underlying mechanism that linking CVD and CKD. However, further investigation by basic and clinical studies is still needed to validate this hypothesis. Although there are plenty of studies focusing on the mechanism and relationship of AS and CVD and CKD, study treating AS in preventing CVD or progression in CKD is limited; future investigations focusing on the treating strategies of AS and its benefits on CVD and CKD are promising.

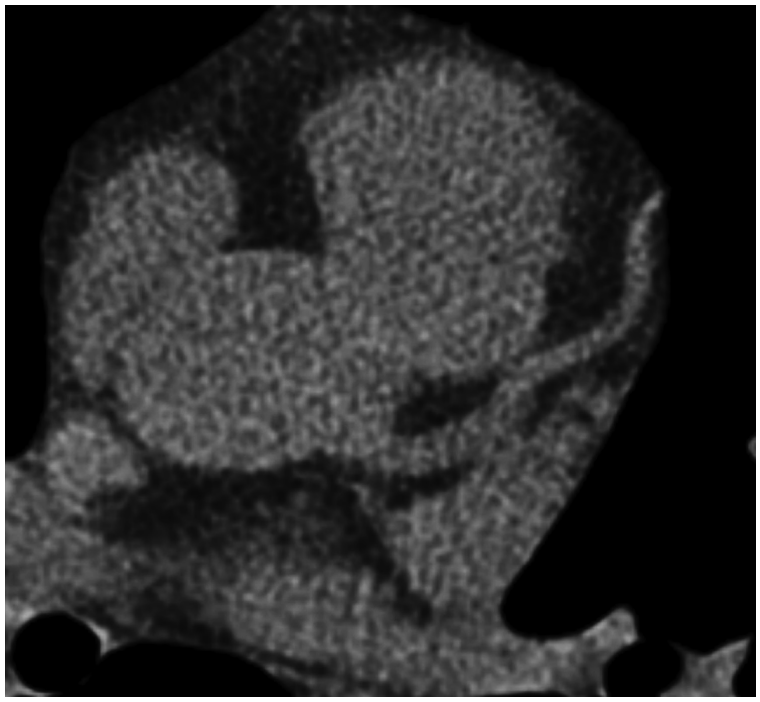
Conflict of interest None.

References available on request Healthcare.India@springer.com

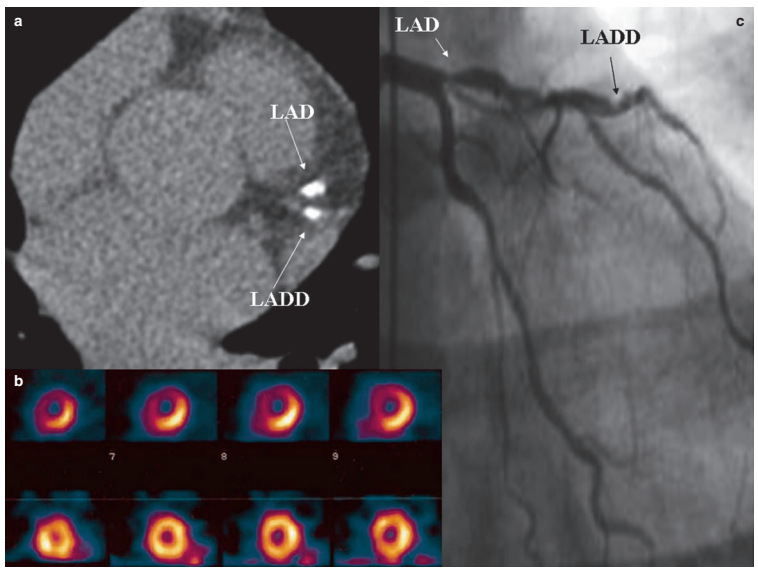
Source: Yuxia Ma, Lin Zhou, Jinghui Dong, et al. Arterial stiffness and increased cardiovascular risk in chronic kidney disease. Int Urol Nephrol. 2015;47:1157–1164. DOI 10.1007/s11255-015-1009-x.

Coronary artery calcium scan

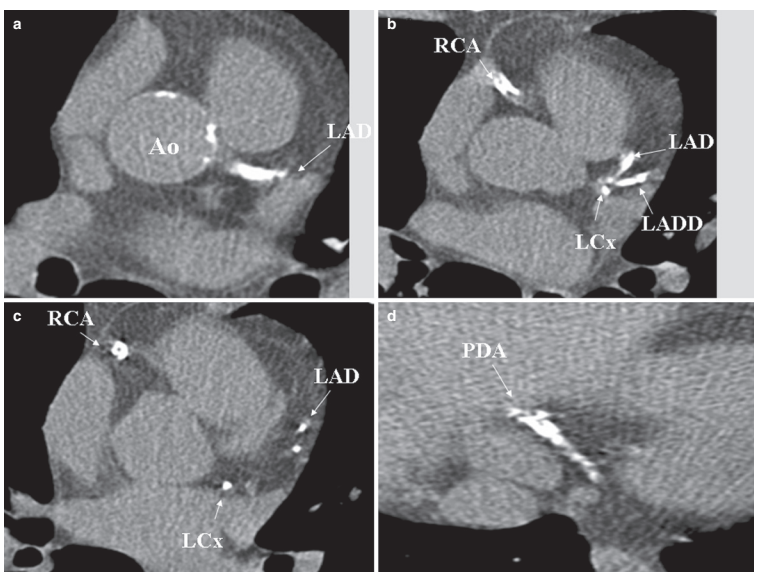
Harvey S. Hecht



A 65-year-old male hypertensive smoker, LDL-C of 140 mg/dL and a 10-year Framingham risk of 25 %. Coronary artery calcium (CAC) scan demonstrated total absence of calcified plaque.



A 41-year-old woman with a premature family history of CAD, total cholesterol 188 mg/dL, LDL-C 112 mg/dL, HDL-C 50 mg/dL, and triglycerides 132 mg/dL, in the lowest Framingham risk group. (a) CAC score of 110, in the left anterior descending and diagonal branch, in the >99th percentile. (b) Dual isotope nuclear stress testing revealing severe anteroseptal ischemia. (c) Angiography demonstrating 95 % ostial LAD stenosis and severe LADD disease. *LAD* left anterior descending coronary artery, *LADD* diagonal branch of left anterior descending coronary artery.



A 57-year-old man with hypertension, total cholesterol 235 mg/dL, LDL-C 150 mg/dL, HDL-C 75 mg/dL, and a 10-year Framingham risk of 12 % referred for CAC scanning; CAC score was 1872, in the >99th percentile. Slices from base (a) through apex (d) reveal significant CAC in all coronary arteries and the ascending aorta. *Ao* aorta, *LAD* left anterior descending coronary artery, *LADD* diagonal branch of left anterior descending coronary artery, *LCx* left circumflex coronary artery, *PDA* posterior descending branch of right coronary artery, *RCA* right coronary artery.

Source: Harvey S. Hecht. Assessment of cardiovascular calcium: interpretation, prognostic value, and relationship to lipids and other cardiovascular risk factors. In: M.J. Budoff, J.S. Shinbane (eds.). Cardiac CT Imaging: Diagnosis of Cardiovascular Disease. Switzerland: Springer International Publishing; 2016.

Q. 1. A 30-year-old African American female student is referred to you for evaluation of hematuria. Urinalysis shows >20 RBCs per high power field. There is no proteinuria. Repeat urinalysis 1 month later shows similar number of RBCs. There are no RBC casts. Her hematuria is unrelated to her menstrual cycle. BP is 120/78 mmHg. Serum creatinine is 1.0 mg/dL. She weighs 60 kg. Renal ultrasound reveals large kidneys with multiple cysts. She wants to know whether or not she has kidney disease. Which one of the following statements is CORRECT regarding her renal condition?

A. She cannot be classified as having chronic kidney disease (CKD) because her serum creatinine is normal
B. She cannot be classified as having CKD because she has no proteinuria
C. She needs a renal biopsy to make the diagnosis of CKD
D. She has CKD based on hematuria and abnormal renal imaging
E. None of the above

The answer is D

In order to provide a uniform definition of CKD, the Kidney Disease Outcome Quality Initiative (KDOQI) of the National Kidney Foundation defined CKD as kidney damage (with or without decreased GFR) or decreased GFR <60 mL/min/1.73 m^2 for >3 months. Kidney damage is defined as pathological abnormalities or markers of damage including abnormalities in blood or urine tests or in imaging studies. Based on the above definition, the patient has microscopic hematuria and large kidneys with cysts. Thus, she is considered to have CKD. Therefore, option D is correct. The eGFR may place her in stage 2 CKD. According to Cockcroft-Gault equation, the calculated GFR is 78 mL/min. She needs follow-up by a nephrologist for evaluation of adult polycystic kidney disease.

The KDIGO (Kidney Disease Improving Global Outcomes) 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease also developed similar criteria to define CKD. In this guideline, CKD is defined as "abnormalities of kidney structure or function, present for >3 months with implications for health." The following table (Table 1) shows the KDIGO recommendations for CKD definition.

Table 1. Criteria for CKD (either of the following present for >3 months).

Criterion	Recommendation
Markers of kidney damage (one or more)	Albuminuria (AER >30 mg/24-h; ACR >30 mg/g; >3 mg/mmol
	Urine sediment abnormalities
	Electrolyte and other abnormalities due to tubular disorders
	Abnormalities detected by histology
	Structural abnormalities detected by imaging
	History of kidney transplantation
Decreased GFR	GFR <60 mL/min/1.73 m^2 (GFR categories G3a–G5)

AER albumin excretion rate, *ACR* albumin:creatinine ratio, *GFR* glomerular filtration rate.

Q. 2. Which one of the following is NOT a traditional risk factor for cardiovascular disease?

A. HTN
B. Diabetes
C. Albuminuria
D. Smoking
E. Dyslipidemia

The answer is C

Except for albuminuria, the remaining factors have been reported as traditional risk factors, as suggested by the Framingham study. The following table lists both traditional and nontraditional risk factors for CKD as well as cardiovascular disease (CVD), suggesting that both CKD and CVD share similar risk factors (Table 2).

Table 2. Risk factors for CKD.

Traditional risk factors	Nontraditional risk factors
Old age	Albuminuria
Male gender	Anemia
HTN	Oxidative stress
High LDL cholesterol	Inflammation
Low HDL cholesterol	Homocysteine
Diabetes	Thrombogenic factors
Smoking	Electrolyte abnormalities (PO^4)
Physical inactivity	
Family history of CKD or CVD	

Source: Alluru S. Reddi. Chronic kidney disease. Absolute Nephrology Review. Switzerland: Springer International Publishing; 2016. DOI 10.1007/978-3-319-22948-5_4.

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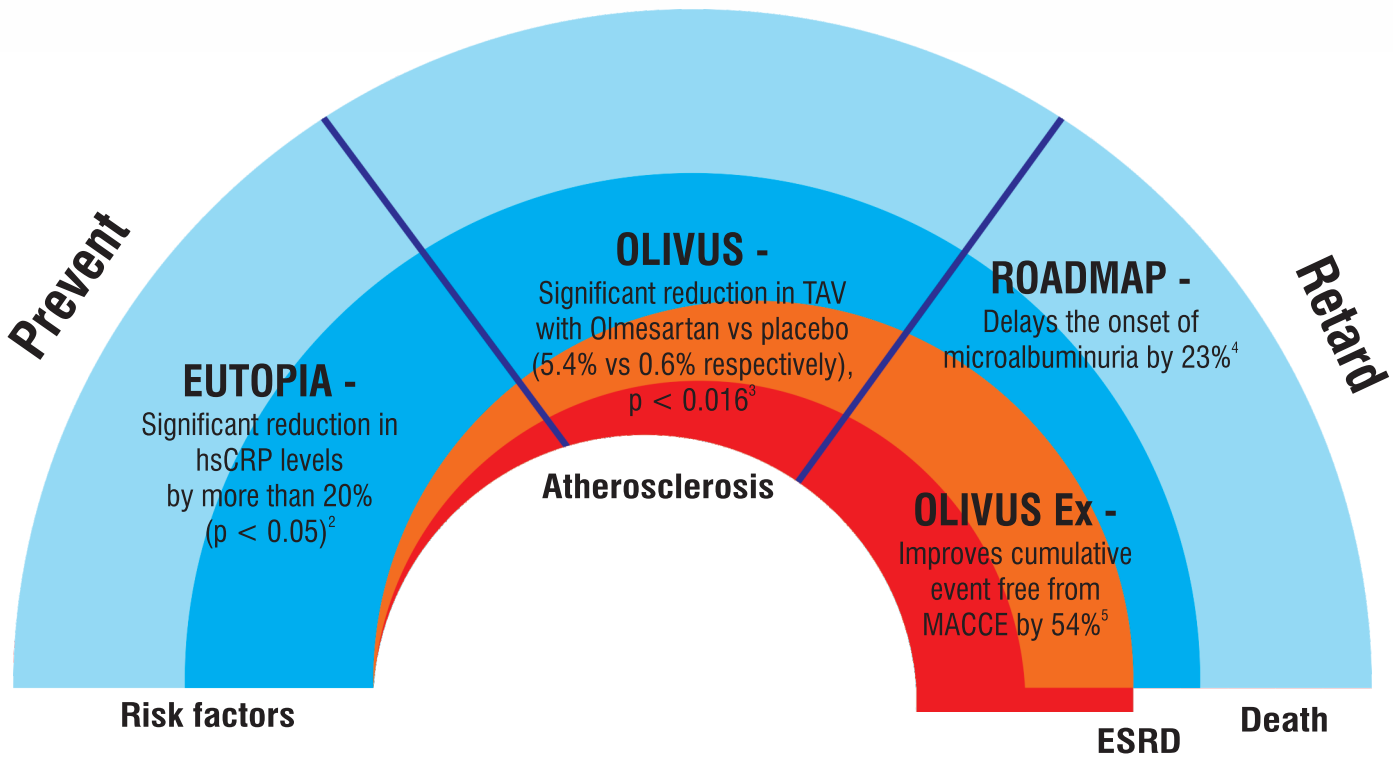

TAV – Total Atheroma Volume, MACCE - Major Adverse Cardio- and Cerebrovascular Events

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