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CORE CONCEPTS

Chronic kidney disease and cardiovascular complications

Cardiovascular diseases such as coronary artery disease, congestive heart failure, arrhythmias and sudden cardiac death represent main causes of morbidity and mortality in patients with chronic kidney disease (CKD). Pathogenesis includes close linkage between heart and kidneys and involves traditional and non-traditional cardiovascular risk factors. According to a well established classification of cardiorenal syndrome, cardiovascular involvement in CKD is known as "type-4 cardiorenal syndrome" (chronic renocardiac). The following review makes an overview about epidemiology, pathophysiology, diagnosis and treatment of cardiovascular complications in CKD patients.

Top stories

Practice updates

Patients with chronic kidney disease (CKD) have heightened risk of developing heart failure (HF), yet few clinical studies have directly investigated the pathophysiologic underpinnings or therapeutic strategies to prevent HF. This article critically reviews the current literature regarding insights in preventing the development and progression of HF in the CKD population.

Prime time news

Not the last word

There are different views on whether white coat hypertensive patients should or should not be given antihypertensive treatment. The present paper reviews four sets of data on the treatment of white coat hypertension, i.e., (1) the lowering effect of antihypertensive drugs on office blood pressure; (2) the concomitant treatment-dependent changes in ambulatory and home blood pressure; (3) the treatment-induced modifications of the so-called white coat effect, i.e., the office-ambulatory or home blood pressure difference; and (4) the ability of blood pressure changes to modify in white coat hypertension the asymptomatic organ damage and the incidence and risk of cardiovascular events.

Cardiovascular imaging

Therapeutic updates

Angiotensin II type 1 receptor antagonists (angiotensin receptor blockers [ARBs]) have been shown to be effective and well tolerated in hypertensive patients. Olmesartan is the seventh angiotensin receptor blocker licensed by the US Food and Drug Administration. The aim of this meta-analysis was to determine the efficacy and tolerability of olmesartan medoxomil in comparison with other ARBs.

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ARTICLE

Chronic kidney disease and cardiovascular complications

Luca Di Lullo, Andrew House, Antonio Gorini, Alberto Santoboni, Domenico Russo, Claudio Ronco

Cardiovascular diseases such as coronary artery disease, congestive heart failure, arrhythmias and sudden cardiac death represent main causes of morbidity and mortality in patients with chronic kidney disease (CKD). Pathogenesis includes close linkage between heart and kidneys and involves traditional and non-traditional cardiovascular risk factors. According to a well established classification of cardiorenal syndrome, cardiovascular involvement in CKD is known as "type-4 cardiorenal syndrome" (chronic renocardiac). The following review makes an overview about epidemiology, pathophysiology, diagnosis and treatment of cardiovascular complications in CKD patients.

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Background

The term known as "cardiorenal syndrome" (CRS) includes a broad spectrum of diseases in which heart and kidney are both involved. The consensus conference of acute dialysis quality initiative group [1] recently proposed the term "cardiorenal syndrome" (CRS) to define the clinical overlap between kidney and heart dysfunction. A clear classification of CRS is crucial as its wide, and appropriate application is required to allow correct interactions between cardiologists and nephrologists.

The CRS classification (Fig. 1) essentially recognizes two main groups, cardiorenal and renocardiac syndromes, on the basis of "primum movens" of disease (cardiac or renal); both cardiorenal and renocardiac syndromes are then divided into acute and chronic, according to the disease's onset. This paper will mainly focus on type-4 CRS: chronic renocardiac and cardio renal syndromes. We will attempt to synthesize and update the most recent knowledge about cardiovascular complications in chronic kidney disease patients.

The type-4 CRS definition itself necessitates the existence of kidney disease before the development of heart failure.

This timing for the diagnosis is not always possible. For example, observational studies such as Acute Decompensated Heart Failure National Registry (ADHERE) conducted on over 100,000 heart failure hospitalized patients probably over-estimated heart involvement in chronic kidney disease patients because of a lack of correct timing in the evaluation of both heart and kidney disease [2–4].

Epidemiological studies have estimated a 13 % CKD prevalence all over the world according to K/DOQI classification [5]. The renal dysfunction represents an independent risk factor for cardiovascular disease, since these patients present higher mortality rates for myocardial infarction and sudden death [5].

Epidemiology

It should now be clear that there is a close relationship between CKD and increased risk of cardiovascular disease: Major cardiac events actually represent almost 50 % of the causes of death in CKD patients [2]. In fact, we find a cardiovascular involvement in each stage of CKD (Table 1), in part due to aging population, and in part linked to higher rates of diabetic, dyslipidemic and hypertensive patients among the CKD population [6]. This can be seen in various studies.

The HEMO Study clearly demonstrated high prevalence (about 80 %) of cardiovascular disease in hemodialysis patients in relation to age, prevalence of diabetes and dialysis duration [3]: Most of the patients were hospitalized for acute coronary syndrome.

Two other studies demonstrated that stage I–IV CKD patients show lower degrees of cardiovascular involvement with respect to dialysis (both hemodialysis and peritoneal dialysis) ones, becoming more evident as GFR falls below 60 ml/min/1.73 m^2 [4, 7].

A meta-analysis by Tonelli *et al.* [8], conducted on 1.4 million patients, found that higher mortality rates for all causes correlated with decreasing eGFR, and the relative death odds ratio was 1.9, 2.6 and 4.4 for eGFR levels of 80, 60 and 40 ml/min, respectively.

The largest epidemiological study was performed by Go *et al.* [9]; they screened over 1 million people identifying cardiovascular events (hospitalization for coronary disease, heart failure, stroke or peripheral artery disease), and all-cause mortality hazard ratio increases according to each declining interval of GFR. After a number of deep multivariable analyses, to avoid the influence of confounding variables (such as traditional cardiovascular risk factors), researchers found that the GFR is a strong, independent factor of cardiovascular morbidity and mortality [9].

Research also shows that cardiovascular risk is particularly evident in CKD patients with stage IIIb–IV (according to K/DOQI CKD classification) and in those who underwent renal replacement therapy—RRT (hemodialysis, peritoneal dialysis and transplant) [10].

In the study by Go *et al.* cited above, the risk of adverse cardiovascular events, compared to the control group with normal GFR, was 43 % higher in patients with GFR between 45 and 59 ml/min/1.73 m^2 and 343 % higher in those with GFR under 15 ml/min/1.73 m^2. Stage V CKD patients, not on renal replacement therapy, showed mortality rates similar to those on dialysis therapy [9]. It is actually possible to estimate that cardiovascular diseases account for 50 % of deaths in CKD patients regardless of biological age [11].

In the Kidney Early Evaluation Program (KEEP) study, there were 100,000 subjects enrolled and screened with a kidney disease and various comorbid disease including congestive heart failure; the resulting data showed an increasing risk of cardiovascular disease of 15 % for every next stage of CKD [12].

The chronic renal insufficiency cohort (CRIC) study investigators focused their attention on 190 CKD patients with GFR <60 ml/min and performed serial echocardiographies; in the 2-year evaluation period during which patients shifted from stage V to end-stage renal disease, ejection fraction (EF) dropped from 53 to 50 % [13].

Cardiovascular events are not only restricted to end-stage renal disease, but early CKD stages are also associated with variable degrees of heart failure as underlined in the atherosclerosis risk in communities (ARIC) population study [14]. The ARIC study wanted to assess the incident cardiovascular events (subjects with preexisting heart failure were dropped out) in about 15,000 subjects. Statistical analysis found an increase in heart failure in subjects with an eGFR less than 60 ml/min/1.73 m^2. Cox analysis demonstrated the relative hazard of incident heart failure by 1.10 in subjects with GFR range of 60–89 ml/min/1.73 m^2 and 1.94 in those with GFR lower than 60 ml/min/1.73 m^2. Furthermore, investigators found that an increase in the albumin to creatinine ratio (ACR) and cystatin C was associated with greater adjusted hazard ratio of heart failure [15].

Considering the epidemiological studies mentioned above, it appears evident that heart failure is particularly prevalent in CKD patients. Moreover, the CKD subjects have a higher mortality risk of cardiovascular disease. Additional support is provided by meta-analysis of 30 cohort studies including

Cardiorenal syndrome classification

Cardiorenal Syndrome (CRS) General Definition: A pathophysiologic disorder of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ
CRS Type I (Acute Cardiorenal Syndrome) Abrupt worsening of cardiac function (e.g. acute cardiogenic shock or acutely decompensated congestive heart failure) leading to acute kidney injury
CRS Type II (Chronic Cardiorenal Syndrome) Chronic abnormalities in cardiac function (e.g. chronic congestive heart failure) causing progressive and potentially permanent chronic kidney disease
CRS Type III (Acute Renocardiac Syndrome) Abrupt worsening of renal function (e.g. acute kidney ischaemia or glomerulonephritis) causing acute cardiac disorder (e.g. heart failure, arrhythmia, ischemia)
CRS Type IV (Chronic Renocardiac Syndrome) Chronic kidney disease (e.g. chronic glomerular or interstitial disease) contributing to decreased cardiac function, cardiac hypertrophy and/or increased risk of adverse cardiovascular events
CRS Type V (Secondary Cardiorenal Syndrome) Systemic condition (e.g. diabetes mellitus, sepsis) causing both cardiac and renal dysfunction

Fig. 1: Classification of cardiorenal syndrome [1].

Table 1: Cardiovascular risk according to chronic kidney disease stage [61].

CKD stage	eGFR (ml/min/1.73 m^2)	Cardiovascular risk (odds ratio)
1	>90	0.5–0.8
2	60–89	1.5
3	30–59	2–4
4	15–29	4–10
5	<15	10–50
ESRD	RRT	20–1,000

CKD chronic kidney disease, *eGFR* estimated glomerular filtration rate, *ESRD* end-stage renal disease, *RRT* renal replacement therapy.

about 40,000 heart failure patients; on a multivariate analysis, serum creatinine levels were found as one of the five most powerful predictive mortality risk factor together with age, ejection fraction, New York Heart Association (NYHA) class and diabetes mellitus [16].

Pathophysiology of heart failure in CKD

Figures 2 and 3 show close interactions between CKD and cardiovascular involvement.

Chronic kidney disease can indirectly (exacerbating ischemic heart disease) and directly (pressure and volume overload leading to left ventricular hypertrophy) contribute to heart disease [17].

Left ventricular hypertrophy is highly prevalent in incident hemodialysis patients and often responsible for subsequent hospitalizations due to heart failure [18]; pressure overload leading to left ventricular hypertrophy results from comorbid conditions such as hypertension and calcific valvular disease [19, 20]. Hyperphosphatemia and secondary hyperparathyroidism (also described as CKD–mineral and bone disorder—CKD–MBD) can induce the ossification of cardiac vessels and valves through "osteoblastic" transformation of vascular smooth muscle cells [21]. Hypertension itself can also contribute to vascular calcification and consequent pressure overload.

Volume overload is mainly supported by CKD secondary anemia and sodium and water retention, and it can be worsened by presence of hemodialysis vascular access [22, 23].

Chronic inflammation, insulin resistance, hyperhomocysteinemia and lipidic dysmetabolism can also contribute to cardiovascular disease in CKD patients. As GFR goes down, the gradual accumulation of a large number of toxins (β2 microglobulin, guanidines, phenols, indoles, aliphatic amines, furans, polyols, nucleosides, leptin, parathyroid hormone and erythropoiesis inhibitors) therefore occurs [24–26].

On the other hand, many other biomarkers increase as GFR declines: troponins, asymmetric dimethylarginine (ADMA), plasminogen-activator inhibitor type I, homocysteine, natriuretic peptides, C-reactive protein (CRP), serum amyloid A protein, ischemia-modified albumin and others [27–29]. All of these are involved in the CKD-related vascular disease development.

B-type natriuretic peptide (BNP) and related N-terminal proBNP (NT-proBNP) are both elevated in CKD patients, as is the case also in subjects with preserved renal function reflecting myocardial cells injured due to hypertension, volume overload, ventricular hypertrophy, cardiac remodeling and fibrosis leading to chamber dilation and pump failure [30, 31].

Impaired heart function leads to renin angiotensin aldosterone system (RAAS) and sympathetic nervous system (SNS) activation with consequent worsening of blood pressure and volume overload [32]; the RAAS and SNS activation can also be responsible for glomerulosclerosis and progressive kidney damage [33, 34].

It is now settled that end-stage renal disease (ESRD) patients develop cardiac fibrosis similar to hypertensive and chronic ischemic heart disease patients in which endocardial and epicardial fibrosis predominate.

Congestive heart failure and myocardial fibrosis

As previously mentioned, echocardiographic abnormalities (impairment of ejection fraction, increased end-systolic and end-diastolic left ventricular diameters and volumes) are frequently reported from the early stages of CKD to end-stage renal disease.

The Landmark study on incident dialysis patients showed how a majority of them had pathologic findings such as systolic dysfunction (15 %), left ventricular hypertrophy (74 %) and left ventricular dilation (36 %) [3, 4].

The hypothetical physiopathological pathway includes blood pressure and volume overload related to the progressive decline of kidney function. Pressure overload is also sustained by coexisting hypertension, valvular heart disease (related to CKD–MBD) and impaired vascular compliance.

The consequent increase in cardiac workload leads to compensatory hypertrophy and excessive myocardial cells stress due to increased oxygen demand leading to myocyte fibrosis and death, heart chambers dilation and systolic dysfunction, as underlined by reduction in ejection fraction [3].

In addition to the hemodynamic mechanisms, the following pathways can also explain the left ventricular hypertrophy and impairment in CKD and dialysis patients: neurohormonal activation, chronic inflammation, malnutrition, endothelial dysfunction and other traditional coronary heart disease risk factors.

Furthermore, in the CKD patients, we observe an accumulation of phosphate due to progressive renal impairment. The hyperphosphatemia leads to an increase in fibroblast growth factor-23 (FGF-23) levels that seem to promote LVH and cardiac remodeling.

The *FGF-23* has paracrine functions in kidneys because of its phosphaturic properties and because it blocks vitamin D3 synthesis. It is also implicated in regulation, growth and differentiation of cardiomyocytes [35].

On the one hand, echocardiographic assays demonstrated a 5 % Left Ventricular Mass Index (LVMI) rise for every log increase in plasma FGF-23 levels and also due to higher rates of valvular calcifications, especially on the mitral valve [36]. On the other hand, it is remarkable how heart failure also develops in patients with lower degrees of CKD as demonstrated by the ARIC study previously mentioned [15] The ARIC study investigators, however, were unable to demonstrate whether the GFR decline occurred before the heart failure onset.

It is now settled that ESRD patients develop cardiac fibrosis similar to hypertensive and chronic ischemic heart disease patients in which endocardial and epicardial fibrosis predominate [37]. Recent evidence suggests that uremic toxins such as indoxyl sulfate and *p*-cresol can contribute to cardiac fibrosis in CKD patients. Indoxyl sulfate concentrations are 300-fold higher than the control population, and this directly contributes to cardiac fibrosis by promoting synthesis of TGF-β, tissue inhibitor of metalloproteinase-1 (TIMP-1) and alpha-1 collagen [38, 39].

Recent studies show an up-regulation of galectin-3, a member of the β-galactoside-binding lectin family synthesized by macrophages and able to interact with extracellular matrix protein like laminin, synexin and integrins. Galectin-3 can bind to cardiac fibroblasts increasing collagen production in myocardium. Recently, Lok *et*

al. enrolled 232 stage IIIa–IV CKD patients and demonstrated that the galectin-3 levels were independent predictors of cardiovascular mortality [39].

Cardiac arrhythmia and sudden cardiac death

Patients with kidney damage are more at risk of cardiac arrhythmia and sudden death, as has been demonstrated in several studies.

CKD patients, especially those undergoing dialysis treatment, are more prone to develop arrhythmias, especially atrial fibrillation and ventricular tachyarrhythmias.

Also, progressive decline of kidney function can lead to impairment of electrolyte homeostasis, particularly involving potassium and calcium blood levels. In cooperation with the electrolytes abnormalities, high rates of coronary disease, hypertension, heart failure and left ventricular hypertrophy can contribute to arrhythmias development.

Significant shifts of electrolytes and changes of blood pressure/volume are common in intra- and inter-dialytic periods leading to a mechanical and electrical dysfunction of myocardial cells, potentially even causing fatal arrhythmias [40]. Research shows that almost half of cardiovascular deaths in end-stage kidney disease population are related to cardiac arrhythmia or sudden death [40]. In this cohort survey on 12,000 prevalent dialysis patients, investigators found that sudden death was accountable for 27 % of deaths while other cardiovascular diseases only for 20 % [40]. This increased risk of sudden death seems to be particularly related to longer dialytic intervals in subjects undergoing hemodialysis treatment three times per week because of extreme shifts of electrolytes and fluids [40].

In another study of over 200 patients enrolled, Chan *et al*. [40] considered linkage between heart rate variability and left ventricular mass finding a close relationship between autonomic dysfunction and left ventricular hypertrophy.

If we consider CKD patients not on renal replacement therapy (RRT), there is evidence that stage II–IV CKD patients undergoing cardiac catheterization show sudden cardiac death mortality rates strongly correlated with the severity of renal disease with a 1.11 hazard ratio for every 10 ml/min/1.73 m^2 fall in GFR [40].

While most clinical studies have been focused on sudden death, investigators have recently given more attention to the prevalence and incidence of atrial fibrillation in CKD and ESRD patients.

Although a minority of dialysis patients with atrial fibrillation receive chronic anticoagulation therapy, this kind of arrhythmia seems to be prevalent, and it can cause thromboembolic stroke and other cerebrovascular accidents. Winkelmayer *et al*. [41] have examined USRDS data on 2.5 million dialysis patients finding an increasing prevalence of medical intervention for atrial fibrillation and reporting a doubling of 1-year mortality in patients with atrial fibrillation versus those without (38.9 vs. 19.3 %).

The burden of atrial fibrillation is therefore complicated due to the increased hemorrhagic risk in this population and to anticoagulation therapy provided during a hemodialysis session [11].

Progressive decline of kidney function can lead to impairment of electrolyte homeostasis, particularly involving potassium and calcium blood levels. In cooperation with the electrolytes abnormalities, high rates of coronary disease, hypertension, heart failure and left ventricular hypertrophy can contribute to arrhythmias development.

As it relates to CKD patients not on dialysis, the reasons for geographic and racial differences in stroke (REGARDS) study drew some important conclusions regarding atrial fibrillation rates in 27,000 subjects [42]. Results showed an increasing rate of atrial fibrillation (ECG-detected) strictly related to CKD degree with a 4–5 % prevalence in stage IV–V CKD patients. After multivariate analysis, the odds ratio for ECG—defined atrial fibrillation–were as follows:

- 2.20 in CKD stage I–II patients,
- 1.51 in CKD stage III patients
- and 2.86 in CKD stage IV–V patients
- (all, respectively, compared to control subjects with normal renal function).

In the chronic renal insufficiency cohort (CRIC) study, the prevalence of atrial fibrillation was 18 % [43].

Coronary atherosclerotic heart disease

CKD patients present increased rates of atherosclerotic coronary disease, acute coronary syndrome, left ventricular hypertrophy and sudden death. These patients also present a higher prevalence of coronary artery disease at angiographic evaluation with multi-vessel disease and ECG evidence of previous ischemia [44, 45]. At this stage, dobutamine stress echocardiography represents the gold standard to perform an artery disease (CAD) screening in renal transplant candidates [46].

Chonchol *et al*. assessed CAD prevalence in early stages of CKD by evaluating coronary catheterization procedures in 261 patients with GFR between 30 and 90 ml/min. The investigators found that more than half of patients with GFR >90 ml/min/1.73 m^2 had a 70 % stenosis in at least one coronary artery and more than 84 % of patients with GFR <30 ml/min/1.73 m^2 showed significant CAD mainly involving the left coronary artery [47]. Atherosclerosis is a condition characterized by the formation of plaques on the intimal layer of vessels, but pathophysiology of vascular disease in CKD is quite different from atherosclerosis-related cardiovascular disease in the general population [48].

In the CKD patients in addition to the traditional risk factors (hypertension, diabetes, dyslipidemia and elderly), there are CKD-related risk factors such as the following:

- endothelial dysfunction (ED),
- hyperphosphatemia,
- secondary hyperparathyroidism,
- vascular calcifications,
- increased oxidative stress and
- chronic inflammation [49];

Therefore, we can assume an alternative pathophysiologic pathway in CKD-related atherogenesis. Systemic persistent inflammation could be the main factor responsible for this increased risk in ESRD, as underlined by raised levels of pro-inflammatory cytokines in renal replacement treatment (RRT). In fact, C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) are higher than in the normal population and in stage I–III CKD patients [50].

The prevalence and influence of vascular calcifications represent the key factor to explain the higher rates of cardiovascular morbidity and mortality in the CKD

population [51]. The presence of vascular calcifications directly affects arterial compliance and coronary circulation with an increase in pulse wave velocity (due to arterial stiffness) and higher incidence of left ventricular hypertrophy [51]. The vascular calcifications usually develop on the median layer of the vascular wall (Monckeberg's sclerosis), and they are typical of CKD patients, in contrast to intimal calcifications of diabetic and chronic ischemic heart disease patients [52]. Medial calcification is characterized by widespread involvement of muscular arteries, such as the tibial and femoral arteries [53].

Malnutrition–inflammation–atherosclerosis–calcification (MIAC) syndrome is characterized by the contemporary presence of chronic inflammation (increased levels of pro-inflammatory cytokines), malnutrition and vascular calcifications in ESRD patients [54]. It has been hypothesized that this is a vicious cycle in which pro-inflammatory cytokines could play a primary role in developing atherosclerotic damage and increasing cardiovascular mortality ratio in hemodialysis and peritoneal dialysis patients [54].

Major cardiovascular events are also predicted by coronary artery calcifications, often already detected before starting RRT [55]. Correlation of coronary artery calcification score (CACS) with coronary flow velocity reserve (CFR) was evaluated in hemodialysis patients [56]: The results pointed out how patients with CACS >10 had lower CFR and worse cardiovascular outcomes [56].

The ESRD patients seem to demonstrate a close relationship between MIAC syndrome development and epicardial adipose tissue (EAT) density [57]. EAT accounts for 20 % of the total heart weight covering about 80 % of the cardiac surface [58]. Although the pathophysiologic role of EAT is still partially unclear, it seems that it may contribute to the chronic inflammatory picture by producing several pro-atherogenic cytokines such as TNF-α, monocyte chemotactic protein-1 (MCP-1), IL-6 and resistin [58].

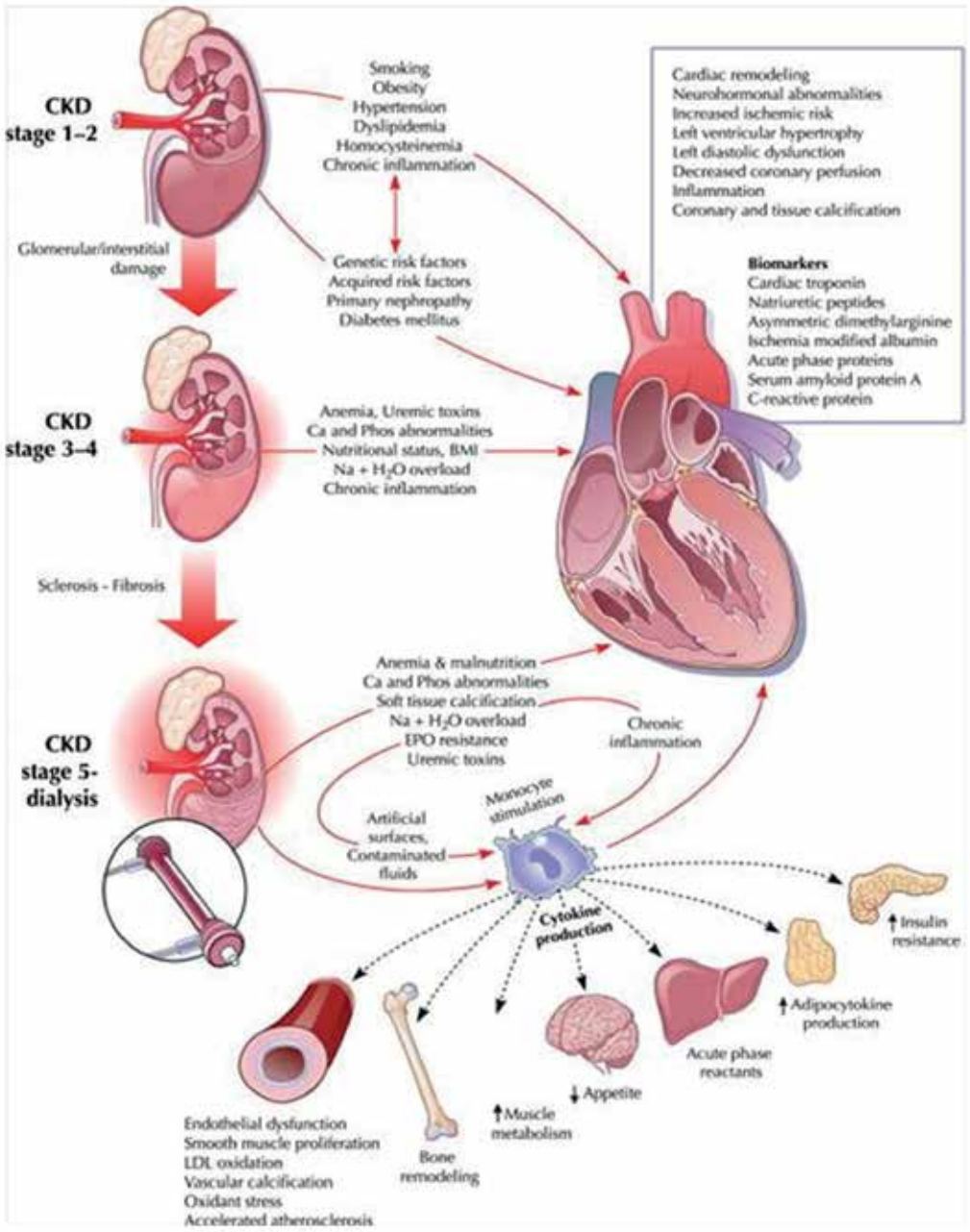

Fig. 2: Pathophysiological pathways of type-4 cardiorenal syndrome [17, 18].

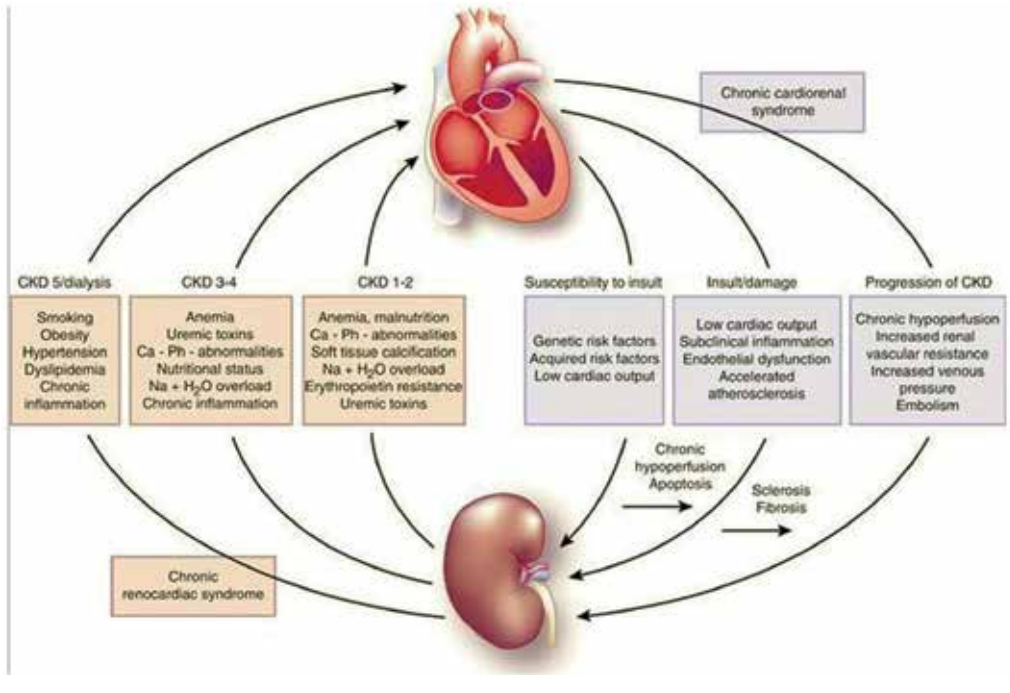

Fig. 3: Clinical correlation between kidney and heart disease [18].

Diagnosis

Cardiovascular involvement in chronic kidney disease can be evaluated by both serological and instrumental tests.

Cardiac function is more widely assessed by NT-proBNP serum levels (as already described in pathophysiology section), while

GFR represents the main biochemical test to evaluate kidney function.

Instrumental diagnosis is mainly based on ultrasound examination of heart (echocardiography) and kidneys (renal ultrasound). An ultrasound examination of the kidneys shows features of chronic nephropathy such as a thin and hyperechogenic cortex with a reduced corticomedullary ratio together with small dilation of the urinary tract; parapyelic and subcortical cysts are also found [59].

Echocardiography can demonstrate signs of volume overload, particularly left ventricular dysfunction and right ventricular dysfunction in ESRD and hemodialysis patients.

Increased atrial volumes or areas (Fig. 4), pleural or pericardial effusion and lung comets are indicators of volume overload [59]. It is quite common to observe valvular calcifications (related to secondary hyperparathyroidism) [59] and frequent right heart dysfunction feature such as high pulmonary artery pressure, low tricuspid annulus plane systolic excursion (TAPSE) or right chamber dilation [60].

Regarding further complications of uremic cardiomyopathy, such as coronary and peripheral artery disease, left ventricular hypertrophy, vascular and valvular calcifications and, finally, myocardial fibrosis, the following tests might be helpful: echocardiography, Doppler ultrasound, computed tomography (CT) and cardiac magnetic resonance (CMR).

Left ventricular hypertrophy is usually assessed by performing standard 2-D echocardiography, although CMR is usually considered the gold standard in correctly evaluating left ventricular mass [61], because it is more accurate in defining left ventricular mass and also in defining volume and pattern of LVH (eccentric, concentric or asymmetric), and assessing fibrosis degree.

If we use the classical M-mode echocardiography in the hemodialysis patients setting, we often over-estimate left ventricular mass compared to CMRI [62] but, on the other hand, CMRI cannot actually be employed widespread due to the costs and the side effects [62].

Because of the clear limits of CMRI, ECHO is still established as the main device by which to evaluate left ventricular mass in daily clinical practice, although there are limitations in determination and quantification of LVH [61]. ECHO accuracy depends on which technique is

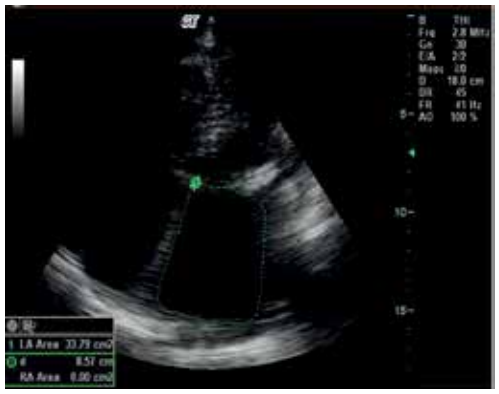

Fig. 4: Left atrium dilation in type-4 cardiorenal syndrome patient [59].

used, the timing of the test relative to the dialysis session and the index used for "normalization" of the data generated. Therefore, ECHO is subject to operator skill, the patients' acoustic windows and errors due to the generation of images when we are in the presence of an asymmetric left ventricular (LV) geometry [62].

The variability in LV mass determination is due to the normalization's index adopted; because the left ventricular mass is proportional to body size, the body surface area value is commonly used to make the correction in classic studies and in clinical practice; so different cutoff values were used in different trials.

Echo and cardiac MRI may be complementary in the evaluation of inter-myocardial fibrosis and diastolic dysfunction in CKD and ESRD patients.

For example, Silverberg used a cutoff value of 125 g/m^2 [63], whereas Parfrey used values from the Framingham study (132 g/m^2 for men and 100 g/m^2 for women) for diagnosis of LVH by ECHO [64].

Recent guidelines redefined normal values of LV mass as <45 g/m height [70, 73] for women and <49 g/m height [65] for men as defined by ECHO [66].

Two-dimensional (2-D) and three-dimensional (3-D) ECHO techniques have also been used to evaluate LV mass in CKD and ESRD, but 2-D echocardiography is based on geometric assumptions and highly dependent on an adequate endocardial and epicardial border definition of the LV. Real-time 3-D allows more precise assessment of LV mass, volume and ejection fraction [66]. In comparison with other methods, 3-D echocardiography demonstrates an accuracy quite close to CMRI [67].

In conclusion, ECHO and CMRI may be complementary in the evaluation of inter-myocardial fibrosis and diastolic dysfunction in CKD and ESRD patients [68]. CMRI has the ability to detect and quantify the presence of myocardial fibrosis, as indicated by late gadolinium enhancement, although it should be avoided in patients with late stages of CKD [69].

CMRI represents the optimal methodology for detecting and quantifying increased LV mass in CKD and ESRD patients, but it is expensive and presents some practical restrictions. Comparatively speaking, the M-mode or 2-D ECHO is more widespread in their employment because they are cheaper and noninvasive techniques (Fig. 5).

A number of noninvasive imaging methods are available to detect vascular calcification and may help clinicians to make therapeutic decisions. Cardiac CT remains the reference standard to detect and quantify coronary artery, aortic and cardiac valve calcifications. However, the high cost of equipment, the inability to perform in-office testing and the expertise required limit its use on a routine basis. Other imaging methods, such as planar X-ray, ultrasound and echocardiography, are appropriate alternatives to evaluate vascular and valvular calcifications [70] (Fig. 6).

As we discussed above, CKD is characterized by widespread atherosclerosis mainly affecting medial layer of the arterial wall, and it is characterized by thickening as a consequence of abnormal collagen production and smooth muscle hypertrophy. Thickening of arterial wall is easily investigated by 2-D echo Doppler ultrasound. Carotid intima-media thickness (IMT) is known as a reliable marker of atherosclerosis and a predictor of cerebrovascular and cardiovascular events [71]. Routine carotid examinations including gray scale and color and pulsed Doppler ultrasound examinations of the left and right common carotid arteries (CCAs) and internal carotid arteries (ICAs) can be conducted. All measurements are made by using angle correction. The peak systolic velocity (PSV), end-diastolic velocity (EDV), Resistive Index (RI) and Pulsatility Index (PI) are always calculated. CKD patients often present higher IMT values together with hemodynamically carotid stenosis, especially in diabetic and polycystic kidney disease patients [72]. Higher IMT

values often suggest the presence of arterial stiffness, which can be confirmed by tonometry techniques, and are closely linked to the presence of uremic cardiomyopathy [73]. CMR allows complete assessment of arterial function through measurement of aortic distensibility (AD). As we know, we can find a reduction in the AD in the early stages of the CKD-related cardiomyopathy natural history [74].

Treatment

At the present time, few randomized controlled trials on heart failure management in CKD patients are available. Several trials on patients with heart failure and coronary syndrome history excluded patients with late CKD stages. Other trials on CKD patients consider as the primary outcome composite cardiovascular endpoints, and not heart failure alone.

Despite these evident limitations, we will focus our attention in this section on available trials on CKD patients seeking to demonstrate the prevention and the treatment of heart failure according to the pathophysiological pathways previously described.

First of all, considering the RAAS system activation in CKD patients (Fig. 5), the RENAAL study is a cornerstone in this field. The RENAAL study was a double-blind, randomized placebo-controlled trial in which investigators aimed to evaluate the renoprotective effects of losartan in over 1,500 type 2 diabetic patients with renal involvement without evidence of heart failure at the baseline [75]. At first hospitalization due to heart failure, the results showed a 32 % reduction in patients treated with losartan.

Also, quite similar to the RENAAL study, the Irbesartan Diabetic Nephropathy Trial (IDNT) study was designed to evaluate the renoprotective effects of irbesartan versus amlodipine or a placebo in over 1,700 patients [76]. Results showed how the irbesartan group had a lower incidence of heart failure compared to the amlodipine and placebo groups [77].

The FOSIDIAL (fosinopril in dialysis) study has evaluated the safety and efficacy of fosinopril on cardiovascular outcomes in almost 400 hemodialysis patients with ecocardiographic findings of left ventricular hypertrophy [78]. Unfortunately, heart failure was not per se evaluated, and the composite endpoint was not statistically significant between fosinopril and the control group.

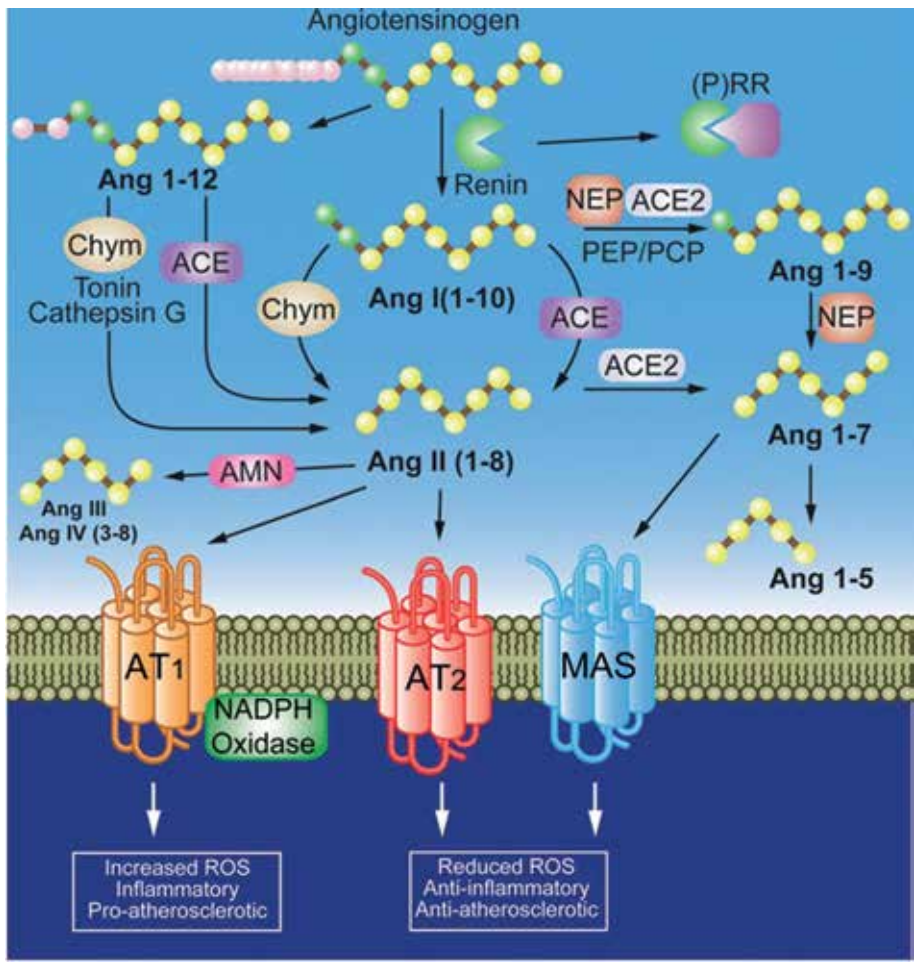

Fig. 5: RAAS (renin angiotensin aldosterone system) activation and blockade in CKD patients [33, 34].

In the Valsartan in Heart Failure Trial (VAL-HeFT) study, patients with class II to IV NYHA were randomly assigned to receive valsartan or a placebo for heart failure therapy, also including ACE inhibition therapy in 93 % of patients enrolled [79]. Patients with serum creatinine >2.5 mg/dl were excluded; about 60 % patients had an estimated GFR <60 ml/min/1.73 m^2 and 8 % presented a proteinuria dipstick positive. Results showed higher mortality and morbidity rates in patients with GFR <60 ml/min/1.73 m^2 and proteinuria, while rates were lower in those with no proteinuria and normal GFR and intermediate in the remaining patients. Therefore, the CKD patients group randomized to valsartan therapy had lower rates of first heart failure hospitalization or death for cardiovascular disease.

Another group of studies focused on the sympathetic nervous system (SNS). A small randomized study on 114 hemodialysis patients affected by dilated cardiomyopathy was performed by Cice *et al.* [80]. Patients were randomly assigned to carvedilol or a placebo in addition to daytime therapy. Primary endpoints included evaluation of left ventricular end-diastolic volume, left ventricular end-systolic volume and ejection fraction (EF) after 24 months randomization. At the baseline, EF was 26 % in both groups; after 24 months, the carvedilol group showed an EF improvement to 37 %, while the placebo group was unchanged at 24 %. Heart failure symptoms improved in carvedilol group that showed lower 2-year mortality rates.

Additionally, the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure (SENIORS study) enrolled CKD patients not on dialysis [81]. In this study,

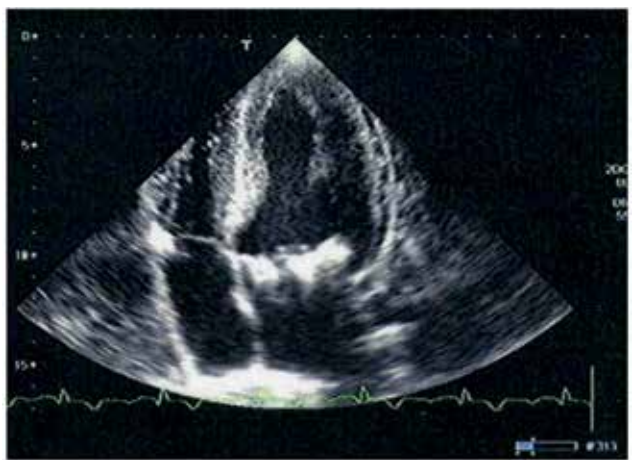

Fig. 6: Four chambers echocardiographic view in ESRD patient showing widespread calcifications of mitral annulus [70].

10 % of patients had normal renal function, while 48 % had stage II CKD and 39 % were stage III CKD. All-cause mortality and cardiovascular disease hospitalizations were reduced in the nebivolol group (31.1 vs. 35.3 % in placebo group), and the effects of nebivolol were also confirmed in the lower GFR patients' group; while no evidence for any relationship between nebivolol and renal function was observed.

The beneficial effects of both RAAS and SNS blockade are consistent in the literature (Fig. 5). The use of beta-blockers plus ACE inhibitors or angiotensin II receptors blockers (ARBs) is associated with better cardiovascular and renal outcomes in elderly patients, also in those with advanced CKD.

The Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) enrolled heart failure patients randomly assigned to treatment with enalapril versus a placebo. There was a marked reduction in mortality [82] together with an increase in creatinine levels (10–15 % with respect to baseline) in the enalapril group, but the effect disappeared when the use of the drug was halted.

Another factor to consider is the close linkage between CKD and MBD and cardiovascular outcomes in CKD patients. The following studies demonstrate this connection.

The Dialysis Clinical Outcomes Revisited (DCOR) trial compared all-cause and cause-specific (cardiovascular and others) mortality in over 2,000 hemodialysis patients (40 % with heart failure at baseline) treated with calcium-based phosphate binders versus sevelamer or calcium-free phosphate binder [83]; in this study, a similar mortality rate was found between groups, and no heart failure outcomes were described.

In the Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events (EVOLVE) trial, 4,000 hemodialysis patients were randomly assigned to cinacalcet or a placebo [84]. A reduction in the frequency of first heart failure was reported in the cinacalcet group, but final results are not exhaustive as underlined by authors themselves.

Di Lullo *et al.* [20] found that treating pre-dialysis patients with sevelamer chloridrate (1,600 mg/day) led to a reduction in cardiac valve calcifications and a delay in kidney function decline occured.

Another fundamental feature in managing cardiovascular complications in CKD patients is dyslipidemia.

The treating to new target (TNT) study allowed post hoc analysis of high-dose atorvastatin therapy in CKD patients [85]; over 3,000 patients with coronary heart disease with GFR <60 ml/min/1.73 m^2 were studied (from a cohort of 10,000) and 12 % of them had heart failure at baseline. The median follow-up period was 5 years, and a first major cardiovascular event was encountered by 9.3 % patients receiving atorvastatin at 80 mg/daily dosage (with concomitant 46 % reduction in hospitalization for congestive heart failure) and by 13.4 % patients receiving atorvastatin 10 mg/daily.

The use of beta-blockers plus angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) is associated with better cardiovascular and renal outcomes in elderly patients, also in those with advanced CKD.

Two trials conducted in ESRD patients were negative, the 4-D trial with atorvastatin [86] and the AURORA trial with rosuvastatin [87]. The SHARP trial actually represents the largest trial on statin employment in CKD patients including 3,023 hemodialysis patients and 6,247 CKD patients not on dialysis. Results clearly showed a significant benefit of the combination simvastatin/ezetimibe on major atherosclerotic events, but all-cause mortality was unaffected [88].

Since left ventricular hypertrophy represents one of most important steps leading to heart chamber dilation, other clinical studies have also tried to examine volemia control employing different hemodialysis strategies. The Frequent Hemodialysis Network (FHN) study [89] randomized 245 patients to three times or six times/weekly hemodialysis for 1 year. The study was not designed to describe differences in major cardiovascular events but showed improvement in ventricular mass measurements in both groups. Further investigations will be needed.

Finally, since a close relationship between anemia and left ventricular pattern [90] has been shown, the treatment of anemia has become a target for treatment trials in CKD patients.

Levin *et al.* [91] did not find statistically significant differences between two groups of CKD patients not on dialysis (immediate versus delayed anemia treatment) regarding left ventricular mass index mean changes.

Meta-analysis involving 1,700 CKD patients (hemodialysis and pre-dialysis ones) concluded that treatment of severe anemia is associated with reduction in left ventricular mass and increasing of ejection fraction [92, 93].

Other trials [94–97] provided evidence that higher hemoglobin levels are often associated with worse outcomes, suggesting that erythropoiesis-stimulating agents (ESA) should not be used to prevent or treat heart failure in CKD patients.

In conclusion, type-4 CRS treatment is mainly based on correction of traditional (hypertension, dyslipidemia, diabetes and obesity) and non-traditional (anemia, chronic inflammation, secondary hyperparathyroidism, LVH, oxidative stress, RAAS and SNS hyperactivity and renal replacement therapy complications) cardiovascular risk factors.

Regarding traditional risk factors, pre-dialysis patients are strongly recommended to contain their blood pressure levels below 130/80 mmHg (ACE inhibitors—ACEi, angiotensin II receptor blockers—ARBs and β-blockers), hemoglobin A1c levels below 7 %, hemoglobin levels between 11 and 12 g/dl and low-density lipoprotein cholesterol below 90 mg/dl (we suggest ezetimibe/simvastatin combination therapy according to the SHARP study), avoiding nephrotoxic drugs and following a low-protein diet (0.6 g/kg/die) [98, 99].

Special consideration should be given to mineral bone disorders preventing hyperphosphatemia (phosphate binders) and vascular calcifications (calcitriol, cinacalcet and paracalcitol) according to KDIGO guidelines [20, 100].

Finally, the treatment of arrhythmias and sudden death represents a new challenge for nephrologists [101] and cardiologists. The use of β-blockers seems to be beneficial while the efficacy of ACEi and ARBs has yet to be proved in further trials [102].

Conflict of interest: All the authors have no conflict of interest to declare.

References available on request
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Source: Luca Di Lullo, Andrew House, Antonio Gorini, et al. Chronic kidney disease and cardiovascular complications. Heart Fail Rev. 2015; 20(3):259–272. DOI 10.1007/s10741-014-9460-9.

Prognostic importance of sodium level trajectory in acute heart failure

Low sodium levels are strongly associated with poor prognosis in acute heart failure (AHF); however, the prognostic impact of the sodium level trajectory overtime has not been determined. A secondary analysis of the AQUAMARINE study in which patients with AHF and renal impairment were randomized to receive either tolvaptan or conventional treatment was performed. Sodium levels were evaluated at the baseline and at 6, 12, 24, and 48 h. We defined 'sodium dipping' as sodium level falling below the baseline level at any time point. The primary endpoint was the combined event of all-cause death and heart failure rehospitalization during follow-up. The analysis included 184 patients with a median follow-up of 21.1 months. Sodium levels more steeply increased during the 48 h in patients without events as compared to sodium levels in patients with events ($P = 0.018$ in linear-mixed effect model). The sodium dipping group ($n = 100$; 54.3 %) demonstrated significantly less urine output, less body weight reduction, and poorer diuretic response within 48 h compared to the non-dipping group. The sodium dipping group was also significantly associated with a low combined-event-free survival after adjustment for other prognostic factors (HR 1.97; 95 % CI 1.06–3.38; $P = 0.033$). The trajectory of sodium levels during the acute phase is associated with the prognosis of patients with AHF independently of the baseline sodium level.

Source: Yuya Matsue, Kenji Yoshioka, Makoto Suzuki. et al. Prognostic importance of sodium level trajectory in acute heart failure. Heart Vessels 1–8. DOI: 10.1007/s00380-017-1020-5. © Springer Japan KK 2017.

Association of angiotensinogen gene SNPs and haplotypes with risk of hypertension in Eastern Indian population

Angiotensinogen (AGT) enzyme comprises a vital module of RAAS system that effectively controls the blood pressure and related cardiovascular functions. Ample association studies have reported the importance of AGT variants in cardiovascular and non-cardiovascular adversities. But lately, owing to the complexity of the many anomalies, the haplotype based examination of genetic variation that facilitates the identification of polymorphic sites which are located in the vicinity of the causative polymorphic site, gets greater appreciation.

In the present study, we have done genotype and haplotype analysis of AGT gene in reference to hypertension to confirm the association of the two in an Indian population. To accomplish this, we performed candidate SNPs analysis and construct possible haplotypes across the AGT promoter and gene region in 414 subjects (256 hypertensive cases and 158 controls).

We found four SNPs (rs11568020: A-152G and rs5050: A-20C in promoter; rs4762 and rs699 in exon2) and 3 haplotypes (H4, H7 and H8) that showed a stronger positive association with hypertension. The haplotype H2 was showing protective association with hypertension.

The results of the present study confirmed and reestablished the role of AGT gene variants and their haplotypes in the causation of hypertension in Indian population and showed that haplotypes can provide stronger evidence of association.

Source: Pulakes Purkait, Kalpataru Halder, Sunil Thakur, et al. Association of angiotensinogen gene SNPs and haplotypes with risk of hypertension in Eastern Indian population. Clin Hypertens. 2017; 23:12. DOI: 10.1186/s40885-017-0069-x. © The Author(s). 2017.

ORIGINAL PAPER

Prevention of heart failure in patients with chronic kidney disease

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Patients with chronic kidney disease (CKD) have heightened risk of developing heart failure (HF), yet few clinical studies have directly investigated the pathophysiologic underpinnings or therapeutic strategies to prevent HF. This article critically reviews the current literature regarding insights in preventing the development and progression of HF in the CKD population.

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Introduction

Cardiovascular disease (CVD) is the leading cause of death in patients with chronic kidney disease (CKD). In fact, individuals with CKD are more likely to die of CVD than to develop progressive renal failure [1, 2]. Since the final common pathway of CVD often leads to the syndrome of heart failure (HF), it is therefore not surprising that HF often complicates the disease course of CKD regardless of stage. Understanding how and why HF develops in the setting of CKD may provide therapeutic opportunities to reduce morbidity and mortality. This article critically reviews the current literature regarding insights in preventing the development and progression of HF in the CKD population.

Epidemiology of heart failure in CKD

Prevalence and incidence

In observational and epidemiological studies, HF prevalence has an inverse relationship with estimated kidney function [3]. Based on the latest US Renal Data System 2013 Annual Data Report, the risk for the development of HF in the Medicare population was higher for CKD patients than for non-CKD patients (42.9 versus 18.5 %) in 2011. This was true across both CKD stages and patient ages (Fig. 1) [4]. Careful longitudinal follow-up of the Atherosclerosis Risk in Communities (ARIC) study investigated the role of impaired kidney

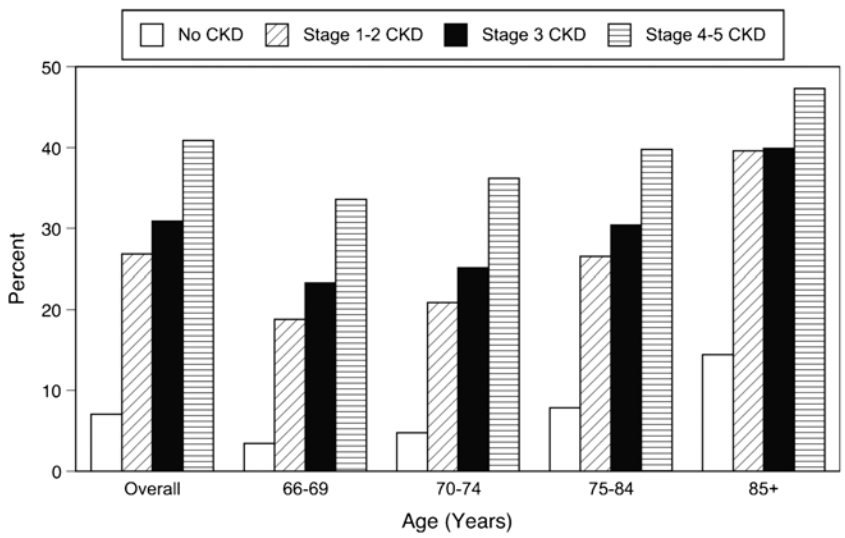

Fig. 1: Prevalence of heart failure by CKD status and age in Medicare population in 2011 (based on data from the US Renal Data System, USRDS 2013 annual data report) [4].

function as a risk factor for incident HF in 14,857 middle-aged individuals without HF [5]. Crude HF incidences were 5.7, 5.9, and 17.7 per 1000 person-years in those with estimated glomerular filtration rate (GFR) ≥90, 60–89, and <60 mL/min/1.73 m^2, respectively.

Mortality

Patients with HF have an increased mortality risk regardless of underlying CKD. Among CKD patients, systolic and diastolic HF have a relative risk of death of 2.34 and 1.93, respectively [4], with a stepwise increase in mortality related to advancing CKD stage. Specifically, patients with systolic and diastolic HF have a 2-year survival of 71 and 72 % for non-CKD, 60 and 65 % for stage 1–2 CKD, and 45 and 50 % for stage 4–5 CKD. This is despite a relatively high utilization rate of guideline-directed medical therapy (52 % angiotensin-converting enzyme (ACE) inhibitors, 67 % beta-blockers, 53 % statins) [4].

Limitations of existing data

There are many potential limitations in establishing the diagnosis of HF in the CKD population. The clinical manifestations of HF can be subtle in the setting of CKD and may even overlap with common signs and symptoms of progressive renal failure—such as fatigue, exercise intolerance, dyspnea, edema, and metabolic derangements and cachexia. Furthermore, in end-stage kidney diseases, such manifestations can be obscured by dialysis therapy where periodic removal of volume and solutes may mask the usual clinical presentations of HF. Meanwhile, the broad and relatively nonspecific clinical definitions of HF allow the descriptive assignment of HF to any progressive signs and symptoms of increased congestion and impaired perfusion as CKD progresses. This may also explain why the prevalence of HF in stage 4–5 CKD, as well as in end-stage renal disease (ESRD), is higher and cannot be validated by database documentations. Echocardiography, therefore, can have a key role in the accurate diagnosis of HF in CKD patients. Despite issues of cost and availability, performing an echocardiogram is reasonable in each CKD patient with cardiac symptoms, new clinical events, or treatments likely to affect LV function. Indeed, recognizing the morbid impact of HF in CKD, the current Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines recommend echocardiograms all CKD 5D patients 1–3 months after renal replacement therapy initiation and in subsequent 3-year intervals, regardless of symptoms [6].

Insights of pathophysiology of HF in CKD from clinical biomarkers

The ability to identify at-risk individuals based on a range of clinical and biochemical features readily available at the bedside may hold the greatest promise in implementing therapeutic strategies for HF prevention. Interestingly, some risk scores for assessing incident risk of HF have serum creatinine, a common marker of kidney function, as part of their configuration [7]. Logically, there is great interest in whether biomarker testing can identify subjects at risk for future adverse HF events in the CKD setting. Specifically, many studies have been conducted to elucidate the association between different clinically available renal and cardiac biomarkers and the development of HF and its adverse outcomes to identify traditional and nontraditional cardiovascular risk factors (Table 1) in extensively phenotyped, community-based populations.

Albuminuria

The appearance of pathological albuminuria often precedes the functional deterioration evidenced by a decline in glomerular filtration rate. Albuminuria has also been shown to be a potent independent marker of an increased risk of HF, even in individuals with few cardiovascular risk factors and a

Table 1: Traditional and nontraditional cardiovascular risk factors in chronic kidney disease.

Traditional risk factors	Nontraditional factors
Older age	Albuminuria
Male sex	Homocysteine
Hypertension	Lipoprotein(a) and apolipoprotein(a) isoforms
Higher low-density lipoprotein cholesterol	Lipoprotein remnants
Lower high-density lipoprotein cholesterol	Anemia
Diabetes	Abnormal calcium/phosphate metabolism
Smoking	Extracellular fluid volume overload
Physical inactivity	Electrolyte imbalance
Menopause	Oxidative stress
Family history of cardiovascular diseases	Inflammation (C-reactive protein)
Left ventricular hypertrophy	Malnutrition
	Thrombogenic factors
	Sleep disturbances
	Altered nitric oxide/endothelin balance
	Elevated cardiac biomarkers (NT-proBNP or cardiac troponin)

urinary albumin-creatinine ratio (UACR) within the normal range. In a contemporary cohort of 10,975 individuals participating in the ARIC Study who were free from HF, a UACR measurement was obtained at baseline and then participants were followed for a median of 8.3 years to assess HF event prevalence [8]. Incident HF was defined as a HF-related hospitalization or death. Compared with normal UACR, the presence of albuminuria was associated with a progressively increased risk of heart failure from intermediate-normal (adjusted hazard ratio [HR], 1.54) and high-normal UACR (adjusted HR 1.91) to microalbuminuria (adjusted HR 2.49) and macroalbuminuria (adjusted HR 3.47). These results were similar to the increased CVD risk with microalbuminuria observed in a community-based elderly cohort [9]. Thus, identification of albuminuria has the potential to facilitate earlier detection of those at an increased risk for the development of HF for preventive therapeutic strategies.

Cystatin C

Serum cystatin C has gained recognition as an excellent endogenous marker of kidney function. Cystatin C is a cysteine proteinase that is produced by almost all human cells and released into the blood. It is freely filtered by the glomeruli and metabolized by proximal tubular cells, but it is not secreted from the tubules. Cystatin C does not appear to be affected by age, gender, or muscle mass, and it has been associated with poor outcomes in the setting of HF [10–12]. Several recent reports have indicated that cystatin C may be a better predictor of adverse cardiovascular (CV) events and all-cause mortality than either serum creatinine or creatinine-based estimating equations [13]. In the Heart and Soul study of 990 ambulatory persons with stable coronary heart disease who were followed for a median of 37 months, subjects in the highest cystatin C quartile (≥1.30 mg/dL) compared with the lowest quartile (≤0.91 mg/dL) had a hazard ratio of 2.6 for incident development of HF, even after adjusting for traditional CVD risk factors [14]. Furthermore, higher cystatin C levels were predictive of HF even among people without microalbuminuria or an impaired GFR as estimated by the MDRD formula (≤60 mL/min per 1.73 m^2). Another community-based, prospective cohort study, the Cardiovascular Health Study, compared serum concentrations of cystatin C and creatinine as predictors of incident HF in 4384 apparently healthy elderly subjects without previous HF [15]. During a median follow-up of 8.3 years, after adjustment for demographic factors, traditional and novel risk factors, CVD status, and medication use, sequential quintiles of cystatin C concentration were associated with a stepwise increased risk for HF in Cox proportional hazards models [15]. In contrast, quintiles of serum creatinine concentration were not associated with incident HF risk in adjusted analysis. Hence, cystatin C concentration appears to be an independent risk factor for HF and appears to provide a better measure of risk assessment than the serum creatinine concentration.

Natriuretic peptides

It is intuitively appealing that natriuretic peptides, which are secreted primarily from cardiac myocytes in response to volume or pressure overload, should be accurate early markers of HF [16]. This has proven true for acutely symptomatic patients, in whom plasma levels of B-type natriuretic peptide (BNP) and its amino terminal fragment (NT-proBNP) are now firmly established as validated diagnostic markers for acute HF and prognostic markers across the spectrum of heart failure stages [16]. Their prognostic and cardiac relevance have also been validated in the CKD and ESRD populations [17, 18]. However, most community-based studies have measured BNP and NT-proBNP levels in patients with preserved renal function, and they are both elevated in the setting of kidney dysfunction even in the absence of underlying HF because their clearance depends on renal function [19]. Nonetheless, BNP and NT-proBNP can be useful in diagnosing HF by using higher cutoffs stratified according to kidney dysfunction. It is worth nothing that the magnitude of increase in NT-proBNP is greater than that of BNP, and NT-proBNP appears to predict HF better than BNP in patients with impaired kidney function [20], although this difference may be subtle. It is also important to note that plasma BNP/NT-proBNP levels frequently change over time even in stable conditions [21]. Therefore, fluctuations may or may not reflect dynamic changes in CVD risk depending on their magnitudes and clinical context. Recent studies have shown that serial measurements of BNP or NT-proBNP provide an incremental risk prediction in acute decompensated or chronic HF settings, with the most recently obtained peptide measurement providing the greatest prognostic value in patients at risk of developing HF [22].

Cardiac troponin

Cardiac enzymes such as creatine kinase (CK) and myoglobin were used for many years as early detection tools for acute myocardial ischemia. Cardiac troponins were introduced because of their increased specificity, but they are also chronically elevated in the setting of CKD, even in the absence of cardiac ischemia [19, 23, 24]. Taking into account the elevated baseline troponin levels in CKD patients, Van Lente *et al*. recommended that a higher threshold of 0.5 μg/L for cardiac troponin T (cTnT) should be used [25], but this has not yet been supported in guidelines. Recent data demonstrated that baseline cTnT levels and changes in cTnT levels measured with a highly sensitive assay are associated with, and can predict, incident HF in individuals without known HF, both independently [26, 27] and in combination with other biomarkers such as NT-proBNP [28]. Indeed, more contemporary data from the Trial to Reduce Cardiovascular Events With Aranesp Therapy (TREAT) study demonstrated that elevated cTnT and NT-pro-BNP levels may identify patients with CKD who are likely to require renal replacement therapy, supporting a link between cardiac injury and the development of ESRD [29].

A simple and effective HF risk score would facilitate the primary prevention and early diagnosis of heart failure in general practice. The ARIC heart failure risk score performs slightly better than the existing risk scores (such as Framingham and Health ABC) in predicting 10-year risk of incident heart failure [30]. The inclusion of NT-proBNP into the risk score markedly improves heart failure risk prediction. A simplified risk score restricted to a patient's age, race, sex, and NT-proBNP performs comparably to the full score and is suitable for automated reporting from laboratory panels and electronic medical records [30]. Another study showed that a simple sex-specific model that includes age, race, cTnT, and NT-proBNP provides a good model, while adding cTnT and NT-proBNP to

clinical characteristics results in an excellent heart failure prediction model [31]. These results strongly suggest that the monitoring of cardiac-specific biomarkers can aid in the prediction and prevention of the development of HF in clinical practice even though they have not been specifically tested in CKD population.

Other biomarkers

Several nontraditional CV risk factors, such as hyperhomocysteinemia, oxidant stress, dyslipidemia, and elevated inflammatory markers, are found in CKD. Recent reviews suggest that oxidative stress and inflammation may be the primary mediators or the "missing links" that explain the tremendous burden of heart failure in CKD. Other factors in CKD are associated with an increased CVD risk as well. For example, iron deficiency is associated with impaired oxidative phosphorylation, and abnormal calcium and phosphorus metabolism are associated with vascular remodeling and the development of noncompliant vessels.

Myeloperoxidase

A major contributor to the increase in circulating inflammatory biomarkers in CKD may be enhanced oxidative stress, possibly involving myeloperoxidase (MPO). MPO is a leukocyte-derived enzyme that can modulate nitric oxide signaling and function resulting in endothelial dysfunction. Systemic MPO was measured in a total of 3733 subjects in the Cardiovascular Health Study who were without a history of prevalent heart failure, myocardial infarction (MI), or stroke [32]. A total of 569 of these subjects developed incident HF during the 7.2 years of follow-up. Patients in the highest MPO quartile showed a higher risk of developing incident heart failure even after adjusting for interim MI, age, gender, systolic blood pressure, smoking, low-density lipoprotein cholesterol, diabetes mellitus, and any subclinical cardiovascular disease (adjusted HR 1.34) [32]. The relationship was more apparent after censoring subjects with incident MI before incident heart failure, even when adjusted for C-reactive protein and cystatin C (adjusted HR 1.46) [32]. Interestingly, stratified analyses showed that the relationship between increased MPO and heart failure risk was stronger in subjects without traditional cardiovascular risk factors. Additionally, an independent association between increased MPO and the development of HF in apparently healthy elderly subjects was observed, particularly beyond myocardial infarction and traditional cardiac risk factors [32]. Thus, increased MPO may predict an increased risk of developing HF.

Ceruloplasmin

Ceruloplasmin (Cp) decreases nitric oxide bioavailability in the blood and has been associated with CVD in clinical studies. In a recent assessment of the association between Cp and incident heart failure in the ARIC study, Cp was measured in 9240 individuals without heart failure or CVD and followed for a mean of 10.5 years [33]. Cp levels were higher in women versus men and were higher in African Americans versus whites. After adjusting for traditional risk factors, high-sensitivity C-reactive protein, NT-proBNP, and high-sensitivity cTnT, higher levels of Cp were associated with heart failure (adjusted HR 1.44) [33]. Another population-based study measured Cp in 6071 men (mean age 46 years) without history of MI or stroke. The incidence of hospitalizations in this population due to HF (primary diagnosis) was monitored over 22 years of follow-up and subjects with myocardial infarction during follow-up were censored. During the follow-up period, 159 men were hospitalized due to HF. Baseline levels of Cp were significantly higher in the men who developed HF and Cp showed a significant association with long-term incidence of HF after adjustment for risk factors [34].

Anemia

Anemia is a special risk factor in patients with CKD. It influences left ventricular hypertrophy (LVH) and dilation, heart failure, and death [35]. Data from the Framingham study found that lower hematocrit was a significant risk factor for the development of symptomatic HF [36]. Therefore, monitoring and preventing anemia in CKD patients may be useful in the prevention of HF.

Preventive therapies of HF in CKD population

Data on the prevention of HF in CKD patients specifically are lacking because patients with significant renal impairment have traditionally been excluded from randomized controlled trials of HF therapies [37]. In the following section, we review strategies for preventing the development of HF in CKD patients based on available studies done within an ESRD population where the endpoints were the incident development of HF or improved primary outcome of HF hospital stay in CKD patients with established HF. Due to lack of studies that specifically report incident HF as an independent outcome or endpoint, composite CV endpoints that included HF as an endpoint are reported.

Lifestyle modifications

It is logical, although unproven, that dietary salt restriction should be a mainstay of clinical counseling. The large majority of "expert opinions" are consistent with strategies advised in any individuals deemed at heightened risk for CVD to prevent HF [38]. Specifically, promotion of a healthy lifestyle, with measures such as smoking cessation, should be encouraged in all patients with any stage of CKD [39]. In addition to primary and secondary cardiovascular benefits in CKD and ESRD populations that can confer more favorable outcomes [40], the modulation of lifestyle risks also confers renal-specific protections. For example, cigarette smoking in CKD accelerates the rate of progression to ESRD potentially via protein carbamylation [41]; therefore, smoking cessation efforts are paramount in preventive strategies [42].

Physical activity and exercise

Increasing physical activity, as part of lifestyle modification, helps decrease the risk of the development of HF in CKD patients. In the Cardiovascular Health Study, plasma NT-proBNP and cTnT levels were measured at baseline and 2 to 3 years later in 2933 non-HF elderly subjects with self-reported physical activity and walking pace documented and combined into a composite score [43]. The investigators found that the probability of an increase in cardiac biomarker concentrations between baseline and follow-up visits was inversely related to the physical activity score. Compared to participants with the lowest score, those with the highest score had an odds ratio of 0.50 for an increase in NT-proBNP and an odds ratio of 0.30 for an increase in cTnT [43]. Although not specifically tested in CKD population,

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CHAPTER

White coat hypertension: to treat or not to treat

Giuseppe Mancia, Rita Facchetti, Michele Bombelli, Guido Grassi, Gianmaria Brambilla, Alberto Zanchetti

There are different views on whether white coat hypertensive patients should or should not be given antihypertensive treatment. The present paper reviews four sets of data on the treatment of white coat hypertension, i.e., (1) the lowering effect of antihypertensive drugs on office blood pressure; (2) the concomitant treatment-dependent changes in ambulatory and home blood pressure; (3) the treatment-induced modifications of the so-called white coat effect, i.e., the office-ambulatory or home blood pressure difference; and (4) the ability of blood pressure changes to modify in white coat hypertension the asymptomatic organ damage and the incidence and risk of cardiovascular events.

Introduction

Three views exist on whether white coat hypertensive patients should or should not be given antihypertensive treatment [1–12]. The first view maintains that because it does not differ from normotension, white coat hypertension needs no therapeutic intervention, the only requirement being remeasurements of in and out-of-office blood pressure, at various intervals after this condition has been detected [1, 2, 10]. The second view points out that in white coat hypertension, cardiovascular risk, although less than in true hypertension, is greater than that of truly normotensive individuals. This suggests an active therapeutic intervention to be limited, however, to lifestyle changes that can improve the adverse risk profile because no evidence exists that antihypertensive drugs are beneficial [5, 6, 9]. The third view acknowledges that the protective effect of antihypertensive drug treatment in white coat hypertension has never been documented. It emphasizes, however, that the high prevalence of this condition makes it likely that white coat hypertensive individuals shared the protective cardiovascular effect seen in trials on mild-to-moderate or elderly hypertensive patients. It thus suggests an extension to these individuals of the same treatment strategy adopted in individuals with either office and home or ambulatory blood pressure elevation, particularly if assessment of organ structure and function shows, as it may not rarely happen, organ damage [3, 12, 13].

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This chapter will review four sets of data on the treatment of white coat hypertension, i.e., (1) the lowering effect of antihypertensive drugs on office blood pressure; (2) the concomitant treatment-dependent changes in ambulatory and home blood pressure; (3) the treatment-induced modifications of the so-called white coat effect [1], i.e., the office-ambulatory or home blood pressure difference; and (4) the ability of blood pressure changes to modify in white coat hypertension the asymptomatic organ damage and the incidence and risk of cardiovascular events.

Antihypertensive drugs and office blood pressure

Several studies have shown that antihypertensive drug treatment can effectively reduce office blood pressure in white coat hypertension. Years ago, this was documented with the use of the alpha-1-blocker doxazosin which lowered office blood pressure in white coat hypertensive subjects to a degree similar to that seen in sustained hypertensives, i.e., in individuals with in and out-of-office blood pressure elevations [14]. It was then reported with the use of a variety of calcium channel blockers [15–18] as well as with different ACE inhibitors [19, 20] and other drugs [21]. An example is given in Fig. 1 which is taken from the European Lacidipine Study on Atherosclerosis (ELSA) on patients with moderate essential hypertension in whom blood pressure was measured in the office and over the 24 h at baseline and at regular intervals during a 4-year treatment period [22]. In patients with office and ambulatory (sustained) hypertension, administration of lacidipine or atenolol caused a marked and persistent systolic and diastolic blood pressure reduction. This was the case, to only a slightly lesser extent, in individuals in whom the normality of ambulatory blood pressure values allowed to detect their belonging to the category of white coat hypertension. The blood pressure-lowering effect was similar when data were separately calculated for the two treatment types (Fig. 2), the only difference

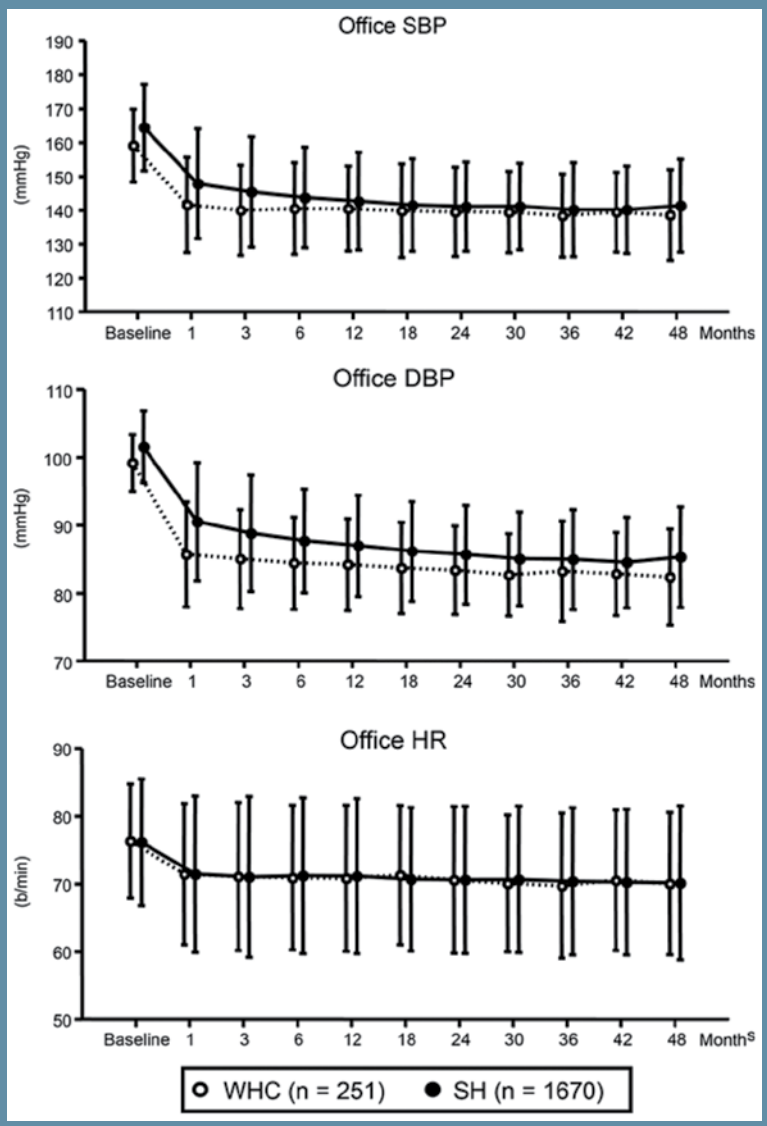

Fig. 1: Office systolic blood pressure (*SBP*), diastolic (*D*) BP, and heart rate (*HR*) values at baseline and during antihypertensive drug treatment (1–48 months) in subjects with white coat hypertension (*WCH*) ($n = 251$) and sustained hypertension (*SH*) ($n = 1,670$). Data are shown as means ± standard deviation. Treatment consisted of the initial administration of lacidipine or atenolol followed if needed by the addition of other drugs.

being an atenolol-related bradycardic effect, which caused some persistent reduction of office heart rate in the overall group of patients as well.

The conclusion that in white coat hypertension office blood pressure can be effectively lowered by antihypertensive drugs independently of its type and mechanism of action is in contrast with a phenomenon that has come to the attention of clinicians and investigators years ago. That is, that in a notable fraction of patients with resistant hypertension, i.e., those in whom three or more antihypertensive drugs administered at adequate doses do not show a satisfactory therapeutic effect, ambulatory or home blood pressure is found to be within their normal limits (Fig. 3), with a cardiovascular risk that is definitively less pronounced than that of resistant hypertensive individuals in whom both in and out-of-office blood pressure is elevated [23–26]. These patients are therefore white coat hypertensives in whom drug treatment does not lower office blood pressure values, no matter how intensive and protracted. As far as the response of office blood pressure to drug treatment is concerned, it thus seems that we have to consider a population of white coat hypertensive individuals who respond to antihypertensive treatment but also a number of patients in whom the elevated office blood pressure values remain persistently high, despite use of multiple medicaments and repeated changes of treatment strategies [13]. The clinical characteristics of the two groups have never been compared, and it is unknown whether the factors responsible for the lower ambulatory or home versus the office blood pressure values differ in the two groups.

Antihypertensive drugs and out-of-office blood pressure

Several years ago the concept has been expressed that in white coat hypertension, drug treatment has no effect on ambulatory blood pressure [1]. This was based on a report of Pickering *et al.* [14] that, although effectively reducing office blood pressure, doxazosin did not have any lowering effect on ambulatory blood pressure values in white coat hypertension. It was also based on studies in which white coat hypertensives were given calcium channel blockers, ACE inhibitors, or other drugs which all caused reductions in office blood pressure without, however, any substantial reduction of day or 24-h blood pressure values [15–19]. However, other observations have turned out not to be entirely in line with the conclusion that in white coat hypertension ambulatory blood pressure is unaffected by treatment. Two studies have reported that the ambulatory blood pressure values of white coat hypertensive individuals were reduced by treatments based on ACE inhibitors, although not by the ones based on calcium channel blockers [19, 20]. Another study has reported a marked and sustained (1 year) reduction of both office and ambulatory blood pressure in black hypertensives treated with long-acting nifedipine [27]. Finally, a recent analysis of the data obtained by the

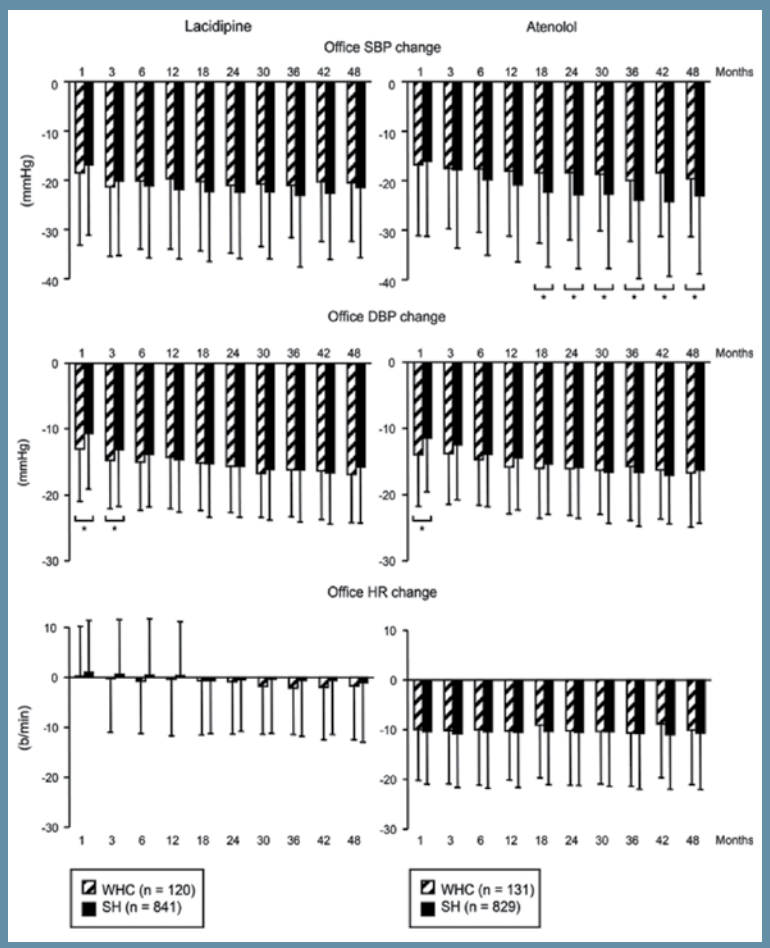

Fig. 2: Office SBP, DBP, and HR changes induced by treatment in subjects with WCH and SH. Data (means ± standard deviation) are shown separately for patients treated with lacidipine and atenolol. Symbols as in Fig. 1.

Hypertension in the Very Elderly Trial (HYVET) on hypertensive patients aged ≥ 80 years has shown that an antihypertensive treatment based on indapamide with the frequent addition of the ACE inhibitor perindopril lowered to a notable degree not only office but also ambulatory blood pressure both in subjects with sustained hypertension and in those defined as white coat hypertensives based on ambulatory blood pressure normality [28].

Detailed evidence on the effect of antihypertensive drug treatment on ambulatory blood pressure in sustained and white coat hypertensive subjects has been provided by a post hoc analysis of the data obtained in the ELSA trial [29] because in this trial all recruited patients underwent an ambulatory blood pressure monitoring at baseline and at yearly intervals over a 4-year treatment period with either lacidipine or atenolol [22]. As shown in Fig. 4, treatment significantly lowered 24-h mean systolic and diastolic blood pressure in sustained hypertension with no loss of the blood pressure-lowering effect throughout the study duration. In striking contrast, ambulatory blood pressure did not exhibit any reduction in white coat hypertensive patients. On the contrary, from the first to the fourth year of treatment, there was a slight but significant progressive increase in the 24-hour (h) mean systolic and diastolic blood pressure values, which at the end of the treatment period were 2.8 and 0.59 mmHg greater than before treatment. This provides strong support to the conclusion that antihypertensive treatment is by and large not capable of lowering ambulatory blood pressure in white coat hypertension. It also provides evidence that the opposite is indeed the case, i.e., that despite drug treatment, there is a tendency for daily life blood pressure values to increase over years.

Why in white coat hypertension ambulatory blood pressure is unaffected by antihypertensive treatment is not clear. The most obvious possibility is that the "law of the initial value" makes the blood pressure reduction achievable by antihypertensive drugs proportionally less pronounced as the baseline blood pressure becomes progressively less, with little no effect when it is normal or low. Indeed, this has been found to occur for ambulatory blood pressure [30], the absence of any treatment-induced fall being predicted at values around 125 mmHg systolic and 80 mmHg diastolic [31]. However, in studies on sustained hypertensives, treatment has been found to be able to lower ambulatory blood pressure to values less than 125/80 mmHg (Fig. 5) [32, 33]. Furthermore, when in the ELSA study white coat hypertensive patients were divided into three groups according to their baseline ambulatory blood pressure values, no treatment-induced blood pressure reduction was seen also in patients with the highest values and thus with more room for a treatment-induced fall [34]. Finally, as mentioned above, in white coat hypertensive individuals, antihypertensive treatment appears to be accompanied not just by no blood pressure-lowering effect but by a blood pressure increase. This may be due to the regression to the mean

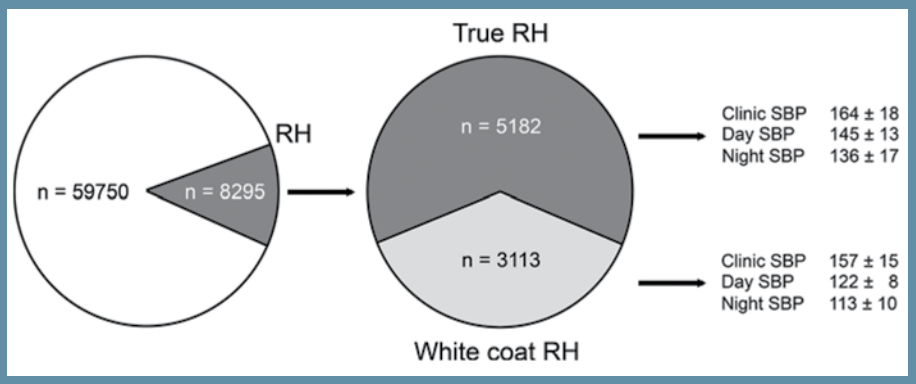

Fig. 3: Prevalence of true and white coat resistant hypertension (*RH*) based on office and ambulatory blood pressure values. True resistant hypertension was defined by office and ambulatory blood pressure elevations, whereas pseudohypertension was defined as elevation in only office blood pressure. Data from about 60,000 patients followed in the clinical practice setting. RH was found in 13.9 % of the hypertensive population. In 37.5 % of them, ambulatory blood pressure was normal (From de la Sierra *et al.* [26], with permission).

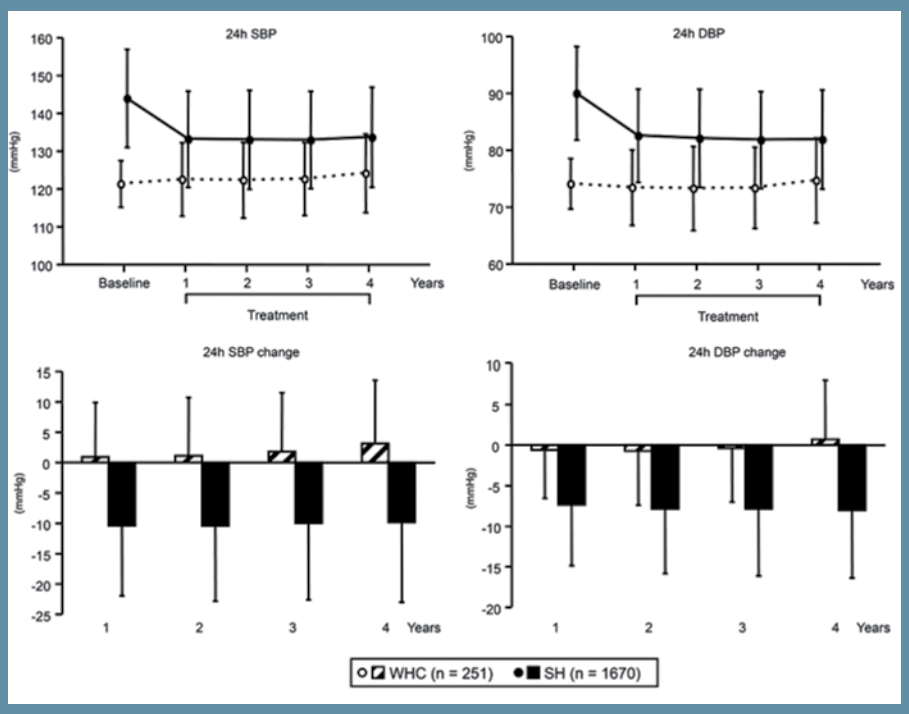

Fig. 4: Twenty-four-hour mean SBP and DBP in white coat and sustained hypertension before and during treatment with lacidipine or atenolol. Data are shown as absolute values (*top panels*) and changes from baseline (*bottom panels*). Changes were calculated by averaging the data provided by the yearly ambulatory BP monitorings ($n = 4$). Symbols as in preceding figures.

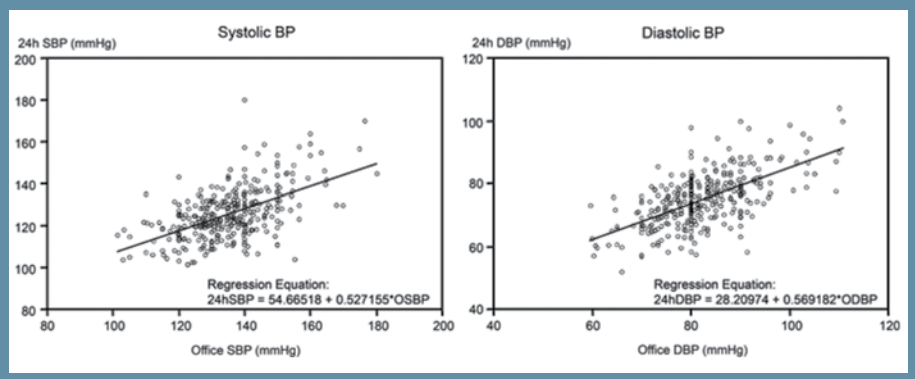

Fig. 5: Relationship between office and 24-hour (h) mean SBP and DBP in the treated hypertensive patients of a mulTicenter study evALuating the Efficacy of Nifedipine GITS–Telmisartan combination in blood pressure control and beyond (TALENT) study. Data refer to a treatment duration of 24 weeks. Treatment consisted of nifedipine GITS and telmisartan. Symbols as in preceding figures (From Mancia *et al.* [32], with permission).

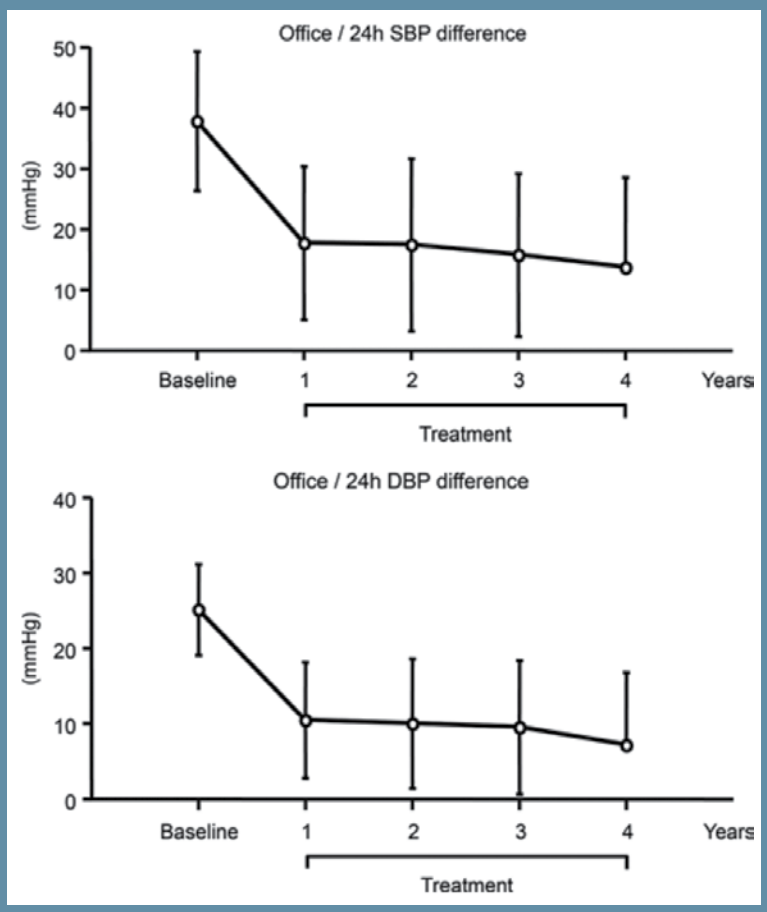

Fig. 6: Office-ambulatory SBP and DBP differences before and during treatment in the white coat hypertensive patients of the ELSA study. Symbols as in preceding figures.

phenomenon, i.e., to the fact that whenever a biological value is low there is a high chance that the following measurement will be higher and vice versa. The possibility also exists, however, that white coat hypertension represents a prehypertensive condition, i.e., that it has a high chance of progressing to sustained hypertension. Verdecchia *et al.* found year ago that 37 % of 83 white coat hypertensives moved to sustained hypertensives over 2.5 years [35]. This has been confirmed by other studies [36, 37], and a much greater risk of white coat hypertensive individuals to develop sustained hypertension has more recently been provided by a 10-year observation period of the PAMELA population [38].

Antihypertensive treatment and white coat effect

Studies on antihypertensive drug treatment agree that the lowering effect is greater for office than for ambulatory blood pressure [39], which means that the office-ambulatory blood pressure difference, i.e., the phenomenon known as the "white coat effect" [1], is usually reduced by treatment. With few exceptions [40], this appears to be the case not only in sustained but also in white coat hypertension [1], a condition in which absence of an ambulatory blood pressure-lowering effect of treatment can make the white coat effect attenuation particularly pronounced. This is exemplified in Fig. 6, which is again taken from the data obtained in the ELSA trial. Patients with white coat hypertension exhibited a marked office-ambulatory blood pressure difference at baseline, but the difference was markedly less pronounced during treatment, consistently over the 4-year duration of the trial.

Does the marked reduction of the office-ambulatory blood pressure difference with treatment just reflect a reduction with time of the alerting response and the office blood pressure rise associated with the doctor's visit? [41]. This is not an easy question to answer because no conclusive evidence exists on the extent to which repetition of the visit attenuates the pressor effect of blood pressure measurements by a doctor [42].It is also uncertain whether the difference between office and ambulatory blood pressure reflects the alerting response to the above-mentioned procedure and thus deserves to be termed the "white coat effect," as commonly done [11]. This has indeed been challenged by a study in which the office-ambulatory blood pressure difference did not exhibit any significant relationship with the white coat effect quantified directly by beat-to-beat blood pressure monitoring before, during, and after the physician's visit [43]. It is made unlikely also by indirect arguments such as that (1) when directly assessed by beat-to-beat blood pressure monitoring before, during, and after the doctor's visit the white coat effect exhibits an increase in both blood pressure and heart rate whereas the office-daytime difference is limited to the blood pressure values [11, 41, 42, 43]. Furthermore, the office-ambulatory blood pressure difference shows a progressive increase with age, but elderly people are not characterized by a hyperreactivity to environmental stimuli, their alerting response to the physician's visit being also similar to that of younger people [41]. Finally, the difference between office and ambulatory blood pressure is not only directly related to office blood pressure but also inversely related to ambulatory blood pressure [44], which is not influenced by the alerting response to blood pressure measurements [45].

Is the attenuation of the office-ambulatory blood pressure difference with treatment then a treatment-related effect, i.e., the consequence of the ability of antihypertensive drugs to lower office more than ambulatory blood pressure? Although data on white coat hypertension are not available, other observations indicate that this is the case. As shown in Fig. 7, compared to the baseline values, the office-ambulatory blood pressure difference was reduced during the

> At present the decision to avoid administration of antihypertensive drugs in white coat hypertension does not only lack appropriate experimental support, but it is also against a number of considerations. One of them is that reduction of office blood pressure by treatment has been indisputably shown to predict patient protection, whereas this has not yet been the case for ambulatory blood pressure changes.

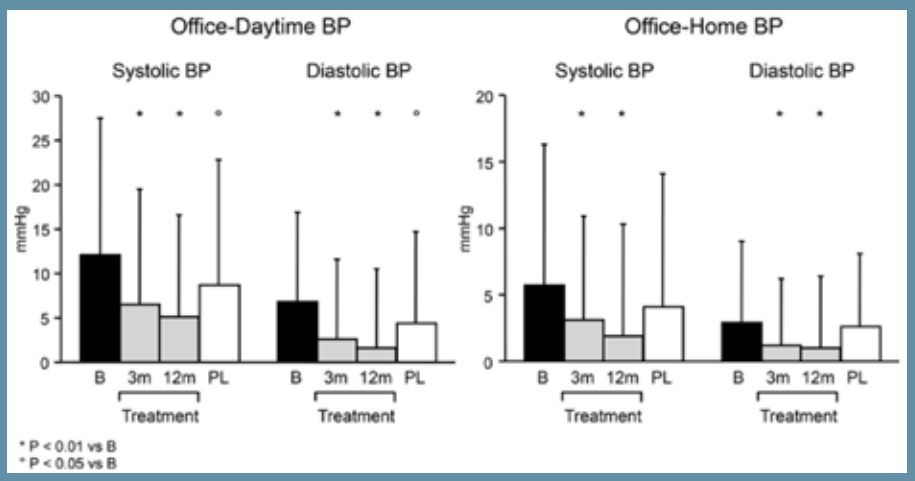

Fig. 7: Office-ambulatory SBP and DBP differences in hypertensive patients in whom the difference was measured before treatment after 3 and 12 months of treatment (an ACE inhibitor with the possible addition of a diuretic) and after a final 1-month period of placebo (From Parati *et al.* [47], with permission).

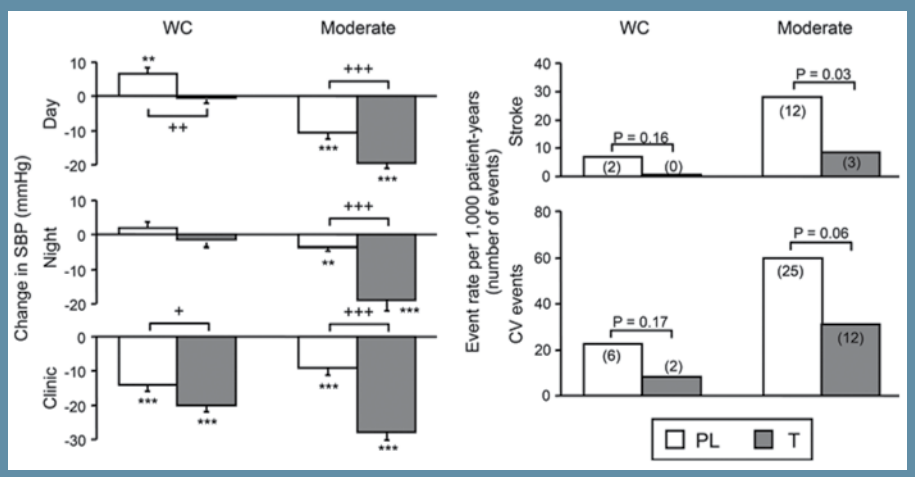

Fig. 8: The *left panels* show the reduction of office (clinic), day and night SBP in a group with a sustained moderate hypertension and a group with WCH. The *right panels* show the rate of stroke and cardiovascular (*CV*) events in either group. Patients were recruited from the SYSTEUR trial on isolated systolic hypertension and belonged to subgroups in which both office and ambulatory blood pressure were measured. Data refer to a placebo (*PL*) group and a group under active drug treatment. $^{*}P \leq 0.05$; $^{**}P \leq 0.01$; $^{***}P \leq 0.001$ of the SBP change vs baseline; $^{+}P \leq 0.05$; $^{++}P \leq 0.01$; $^{+++}P \leq 0.001$ between PL and T groups (From Fagard *et al.* [48], with permission).

visits performed after 3 and 12 months of antihypertensive treatment. There was, however, a recovery during a final month of placebo which proved that the previous attenuation was at least in part due to the differential effect of the drugs employed on in and out-of-office blood pressure [46, 47].

Antihypertensive treatment and cardiovascular protection

Ultimately, whether treatment is protective on patients with white coat hypertension needs documentation from prospective studies having a proper control group and outcomes of undisputable prognostic significance as endpoints. At present, no such studies have been performed, and the only available evidence is the one obtained from limited number of patients with isolated systolic hypertension recruited from the Systolic Hypertension in Europe trial (SystEur) in whom also ambulatory blood pressure data were collected [48]. Compared to the placebo group, patients with sustained hypertension showed a reduction of office blood pressure, ambulatory blood pressure, and cardiovascular morbid and fatal events. In contrast, white coat hypertensive patients only exhibited an office blood pressure reduction, the nonsignificant fall in ambulatory blood pressure being accompanied by a more modest and nonsignificant reduction of cardiovascular morbidity and mortality as well (Fig. 8). However, the study could count on only few events in each group which limited the statistical power to detect between-group differences and made the conclusion that antihypertensive treatment may carry little benefit in individuals in whom blood pressure elevations are limited to office values only tentative. This limitation is shared by the other available evidence, i.e., the one provided by the post hoc analysis of the ELSA trial in which the cumulative 4-year incidence of cardiovascular morbidity and mortality showed a similar slope in white coat and sustained hypertensive patients.

Deciding that white coat hypertensive patients can be spared antihypertensive drugs would be of great practical importance because this condition is common and may account for up to 40 % of the mild and elderly hypertensive population [21, 43]. Demonstration that treatment is unnecessary would thus substantially reduce healthcare costs. However, at present the decision to avoid administration of antihypertensive drugs in white coat hypertension does not only lack appropriate experimental support, but it is also against a number of considerations. One of them is that reduction of office blood pressure by treatment has been indisputably shown to predict patient protection, whereas this has not yet been the case for ambulatory blood pressure changes. Furthermore, the high prevalence of white coat hypertension means that this condition might have shared the protective effects of antihypertensive treatment repeatedly demonstrated in randomized trials, those on mild hypertension and hypertension in the elderly in particular. This has been recently suggested by the results of the HYVET trial on octogenarian hypertensives which have shown that (1) white coat hypertension accounted for more than 50 % of the recruited population [28] and (2) only an involvement of white coat hypertensive individuals could explain the beneficial effects of treatment in the overall patients of the trial [49]. As mentioned by the recent guidelines on hypertension of the European Society of Hypertension and the European Society of Cardiology, sufficiently powered randomized controlled trials are needed to provide undisputable evidence on this issue [13].

References available on request Healthcare.India@springer.com

Source: Giuseppe Mancia, Rita Facchetti, Michele Bombelli, et al. White coat hypertension: to treat or not to treat. In: Giuseppe Mancia, Guido Grassi, Gianfranco Parati, Alberto Zanchetti (eds). White Coat Hypertension: An Unresolved Diagnostic and Therapeutic Problem. 1st ed. Switzerland: Springer International Publishing; 2014, pp 123-135. DOI 10.1007/978-3-319-07410-8_8.

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these findings indirectly suggest that a higher activity score is associated with a lower long-term incidence of HF.

Angiotensin-converting enzyme inhibitors

ACE inhibitors are perhaps the only HF drug class that has been prospectively studied and clinically indicated for the prevention of HF in at-risk patients. The Fosinopril in Dialysis (FOSIDIAL) study was the first prospective controlled to analyze ACE inhibitor treatment in ESRD patients [44, 45]. No significant benefit for fosinopril treatment was observed in regard to endpoint reduction (Table 2). However, there was a baseline imbalance between the two study arms, with a higher prevalence of cardiovascular disease in the fosinopril arm. Thus, it is possible that the negative outcome of this trial may be at least partially explained by suboptimal randomization. In contrast, a study using benazepril in advanced HF patients in China found a significant reduction in progression in renal insufficiency even in creatinine ranges that precluded its usage [46]. Whether this may also have HF protective effects was not investigated. Meanwhile, a re-analysis of the Heart Outcome Prevention Evaluation (HOPE) study was performed to evaluate the contribution of ACE inhibition in HF protection in 9297 high-risk patients who were randomly allocated to receive ramipril or a placebo. Ramipril significantly reduced the number of HF hospitalization events (11 versus 21 per 1000 patient-years) in the subgroup of patients with renal insufficiency (serum creatinine ≥1.4 mg/dL) [47]. These results parallel with the overall cohort in terms of reducing HF hospitalizations [48] as well as the reduction in risk of progression of albuminuria [49] in the main HOPE study.

Angiotensin receptor blockers

Takahashi *et al.* investigated whether candesartan at a dose of 4–8 mg/day (versus no treatment) can reduce the incidence of cardiovascular events (including HF) in patients undergoing hemodialysis (Table 2). During the follow-up period of 19.4 months, seven patients (16%) in the candesartan group versus 17 patients (46%) in the control group had cardiovascular events [50]. Some details of the study cohort warrant special attention as they limit the ability to extrapolate these findings to the general ESRD population: a history of overt cardiovascular disease was an exclusion criterion and the study population's body mass index was low (mean 20.5 kg/m^2) as was the mean hemoglobin level (~9 g/dL). Meanwhile, in a post hoc analysis of the Telmisartan Randomized Assessment Study in ACE Intolerant Subjects With

Table 2: Selected clinical studies to reduce cardiovascular events in chronic kidney diseases.

Study	Primary endpoint	RR	HR	OR	95% CI	*P* value
Besarab *et al.* [83]	Death or MI high- versus low-hematocrit group	1.3	–	–	0.9–1.9	N.S.
SPACE [69]	MI, IS, PVD, and unstable AP	0.46	–	–	0.27–0.78	0.014
Tepel *et al.* [70]	MI, CVD death, need for coronary angioplasty or coronary bypass surgery, IS, PVD with amputation or need for angioplasty	0.6	–	–	0.38–0.95	0.03
Cice *et al.*[a][56, 57]	Changes in LVEDV, LVESV, LVEF, and clinical status 24 months after randomization	n.r.	n.r.	n.r.	n.r.	n.r.
Wrone *et al.*[b] [80]	Cardiovascular events (i.e., MI, stroke, coronary artery intervention, limb amputation, carotid endarterectomy, TIA) and mortality	n.r.	n.r.	n.r.	n.r.	N.S.
4D [59]	Death from cardiac causes, nonfatal stroke, nonfatal MI	0.92	–	–	0.77–1.1	0.37
FOSIDIAL [45]	Combined fatal and nonfatal first major cardiovascular event (CV death, resuscitated death, stroke, HF, MI, revascularization)	0.93	–	–	0.68–1.26	0.35
Svensson *et al.* [65]	Cardiovascular event or death (i.e., acute MI, AP that required coronary investigation or intervention or death, IS, TIA, PVD that required surgical intervention or death)	–	1.04	–	0.72–1.48	0.85
ASFAST [79]	Rate of progression of intima media thickness, composite of MI, stroke, and CV death	–	0.98	–	0.66–1.47	0.94
Takahashi *et al.* [50]	MI, unstable AP, HF, severe arrhythmia, sudden death	–		0.23	0.08–0.67	<0.01
HOST [76]	Death from any cause	–	1.04	–	0.91–1.18	0.6
Vianna *et al.* [78]	Death from cardiovascular causes, MI, cardiac arrhythmias, AP, HF, cerebral vascular accident	–	0.98	–	0.74–2.1	0.41
Suzuki *et al.* [52]	CVD death, MI, stroke, HF, coronary artery bypass, grafting, or percutaneous intervention	0.51	–	–	0.33–0.79	0.002
AURORA [60]	Major cardiovascular event (i.e., nonfatal MI, nonfatal IS, death from cardiovascular causes)	–	0.96	–	0.84–1.11	0.59
Heinz *et al.* [77]	Total mortality	–	1.13	–	0.85–1.5	0.51
SHARP [61]	Major atherosclerotic events[c] (i.e., nonfatal MI, coronary death, nonhemorrhagic stroke, arterial revascularization excluding dialysis access procedures)	0.83	–	–	0.74–0.94	0.0021

AP angina pectoris, *CI* confidence interval, *CVD* cardiovascular disease, *CHF* congestive heart failure, *HF* heart failure, *HR* hazard ratio, *n.r.* not reported, *N.S.* nonsignificant, *IS* ischemic stroke, *LVEF* left ventricular ejection fraction, *LVEDV* left ventricular end-diastolic volume, *LVESV* left ventricular end-systolic volume, *MI* myocardial infarction, *OR* odds ratio, *PVD* peripheral vascular disease, *RR* relative risk, *TIA* transient ischemic attack

[a]Cice *et al.* defined the primary endpoint as continuous changes in predefined parameters (not in dichotomized categories as changes above or below certain cutoffs)

[b]Wrone *et al.* did compare three treatment groups (i.e., 1, 5, and 15 mg folic acid) and did not observe significant differences in their composite primary endpoint between the three groups ($P=0.47$; log-rank test)

[c]The primary endpoint was changed after the first year

Cardiovascular Disease (TRANSCEND) trial, there was an observed benefit on CVD events with telmisartan versus placebo in all renal subgroups (primary outcome was a composite of myocardial infarction, stroke, cardiovascular death, or HF hospitalization) [51]. However, in a similar analysis of the Ongoing Telmisartan Alone and in Combination With Ramipril Global End Point Trial (ONTARGET) trial, there was no difference in cardiovascular outcomes between ramipril, telmisartan, or both in any renal subgroup [51]. Hence, the authors concluded that dual therapy was not more effective than monotherapy. In patients undergoing hemodialysis, Suzuki *et al.* analyzed the effect of angiotensin receptor blocker (ARB) treatment using different ARBs versus no treatment (control group) on cardiovascular events [52]. The authors reported a significant effect of ARB therapy on the primary endpoint (Table 2). However, this study was conducted in a cohort of patients with a low prevalence of coronary artery disease (CAD) (4%) and HF (16%). The usage of β-blockers was low (4%) and the usage of ACE inhibitors was an exclusion criterion. Hence, whether routine ARB should be used (especially in place of ACE inhibitors) is still not clear.

Mineralocorticoid receptor antagonists (MRA)

In CKD stage 3 patients, convincing evidence for the use of MRAs comes from the recent Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) trial, where 33% of HF NYHA II patients had estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 [53]. The effect of eplerenone on the primary composite endpoint of HF hospital stay or cardiovascular death was consistent in patients dichotomized at an eGFR <60 mL/min/1.73 m^2; eplerenone improved outcome irrespective of renal function [54]. A recent multicenter prospective randomized 3-year study using spironolactone treatment versus control group in 309 oliguric ESRD patients on hemodialysis showed that the primary composite outcome of death from cardiovascular and cerebrovascular events or hospitalization occurred in 5.7% of patients in the treatment group and in 12.5% of patients in the control group (adjusted HR 0.379). The secondary outcome of all-cause mortality was significantly reduced in the treatment group compared with the control group (6.4 versus 19.7%; adjusted HR 0.335). These promising findings warrant further investigations, especially regarding its impact on HF development and progression.

Beta-adrenergic receptor antagonists (Beta-blockers)

The rationale for using beta-blockers in patients with advanced CKD or ESRD is targeting uremic "sympathetic overactivity." In a recent post hoc analysis of 4217 CKD patients, treatment with carvedilol decreased the risk of first hospitalization for HF (HR 0.74) and the composite of cardiovascular mortality or HF hospitalization (HR 0.75) [55]. Meanwhile, carvedilol therapy has been associated with significant improvement in left ventricular volumes, ejection fraction, HF symptoms, and long-term outcomes in hemodialysis patients with dilated cardiomyopathy (LV ejection fraction <35%) who were already on ACE inhibitors [56, 57].

In a post hoc analysis of the Telmisartan Randomized Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease (TRANSCEND) trial, there was an observed benefit on CVD events with telmisartan versus placebo in all renal subgroups (primary outcome was a composite of myocardial infarction, stroke, cardiovascular death, or HF hospitalization).

Cholesterol-lowering therapies

In nonrenal patients, statin therapy consistently reduces the incidence of CVD events and mortality in patients at high cardiovascular risk [58]. Three prospective interventional trials dealing with statin therapy in ESRD patients have been conducted. The first two studies, 4D (Deutsche Diabetes Dialyse Studie) [59] and AURORA (Assessment of Survival and Cardiovascular Events) [60], both showed no benefit in dialysis patients despite significant reductions in low-density lipoprotein (LDL) cholesterol levels (~40% in both studies). The third study, the Study of Heart and Renal Protection (SHARP) trial, included approximately 6000 CKD and 3000 ESRD patients with a mean follow-up of 5 years. Patients were assigned to receive either 20 mg simvastatin plus 10 mg ezetimibe or a placebo. In contrast to 4D and AURORA, the SHARP study was designed as a trial for primary prevention since a history of CAD was an exclusion criterion. The combined atherosclerotic endpoint (nonfatal myocardial infarction or coronary death, nonhemorrhagic stroke, or arterial revascularization) exhibited a relative risk reduction of 17% compared with placebo irrespective of CKD stage [61]. Hence, the latest KDIGO guidelines recommended the use of statin or statin/ezetimibe treatment in adults aged 50 years or above with estimated glomerular filtration rate <60 mL/min per 1.73 m^2 but not treated with chronic dialysis or kidney transplantation [62]. Whether this can lead to HF prevention has yet to be demonstrated, although in the HF literature, early intervention has been associated with better outcomes even though statin use was not clinically indicated for the purpose of preventing adverse events in HF [63].

N-3 Polyunsaturated fatty acids

N-3 polyunsaturated fatty acids (*n*-3 PUFA) have been shown to reduce plasma lipids, lower blood pressure, and exhibit anti-atherosclerotic, antithrombotic, anti-inflammatory, and anti-arrhythmic properties [64]. Svensson *et al.* conducted a randomized, double-blind, placebo-controlled intervention trial comparing the effect of *n*-3 PUFA and a control treatment as secondary prevention of cardiovascular events in 206 ESRD patients with documented CVD undergoing hemodialysis [65]. Although they could not report a significant reduction in total cardiovascular events and death, they observed a significant reduction in the number of myocardial infarctions in the *n*-3 PUFA-treated group (HR 0.3) [65]. The potential benefits for *n*-3 PUFA have also been questioned in the general population with multiple CVD risk factors, with the daily use of *n*-3 PUFA therapy failing to reduce cardiac morbidity and mortality [66]. It is also worth considering the potential risk of bleeding with PUFA therapy when determining the usefulness of this treatment option.

Antioxidant therapies

Oxidative stress has been considered a potential therapeutic target for HF prevention [67]. In CKD, heightened oxidative stress has long been associated

with increased cardiovascular risk [68]. The Secondary Prevention with Antioxidants of Cardiovascular disease in End-stage renal disease (SPACE) study tested whether oral treatment with vitamin E reduces the incidence of cardiovascular events in ESRD patients with preexisting cardiovascular disease [69]. The result was a significant reduction (−47 %) in the primary endpoint (myocardial infarction, peripheral vascular disease, or unstable angina) by vitamin E treatment. Additionally, a small, monocentric study by Tepel *et al.* also showed that acetylcysteine significantly reduced cardiovascular events [70]. These promising small studies have yet to be integrated with the notion that antioxidant therapy does not reduce the risk of cardiovascular and all-cause death or major cardiovascular events in the broader population [71].

Vitamin D supplementation

Patients with CKD have reduced vitamin D levels for several reasons, including a lack of sunlight exposure, increased loss of vitamin D metabolites in the urine, and reduced renal secretion of 1,25-dihydroxyvitamin D, driven first by elevated fibroblast growth factor 23 (FGF-23) levels which directly inhibit 1-alpha-hydroxylation and second by the loss of renal tubules containing 1-α-hydroxylase, the enzyme from which active vitamin D is synthesized [72]. Vitamin D deficiency has been proposed as a target in cardiovascular disease, with a number of observational studies demonstrating a strong association between correcting the deficiency of vitamin D and a decrease in cardiovascular risk [73]. PRIMO is a randomized controlled trial investigating the effects of the active vitamin D (paricalcitol 2 μg/day) versus placebo on left ventricular mass over 48 weeks in patients with an estimated GFR of 15–60 mL/min/1.73 m^2 [74]. At 48 weeks, the change in left ventricular mass index and measures of diastolic dysfunction did not differ between treatment groups [74]. Hence, there remains limited evidence to substantiate the role of vitamin D supplementation in preventing HF in CKD [75].

Homocysteine-lowering therapy

As CKD patients with high cardiovascular mortality rates often exhibit greatly increased homocysteine concentrations, a homocysteine-lowering therapy was thought to positively affect the incidence of cardiovascular events in the CKD population. Indeed, CKD patients in the Homocysteinemia in Kidney and End-Stage Renal Disease (HOST) study achieved a significant reduction in their homocysteine level (−26 %) by oral treatment with folic acid, pyridoxine hydrochloride, and vitamin B_{12} compared with the placebo group, yet this did not translate into better outcomes [76]. Heinz *et al.* also combined vitamin B_{12} and folic acid. Despite a significant reduction in homocysteine (−35 %), there was no significant effect on the risk of cardiovascular events [77]. Of note, two other RCTs (Vianna *et al.* [78] and ASFAST [79]) compared folic acid treatment with placebo and one trial (Wrone *et al.* [80]) compared different dosages of folic acid in ESRD patients. Again, all three failed to show a significant effect on their primary endpoint (composite of cardiovascular events). At present, there is no role for homocysteine-lowering therapies in reducing CVD events.

Increasing hemoglobin by erythropoiesis-stimulating agents (ESA)

Partial anemia correction (aiming for hemoglobin levels >10 g/dL) has been shown to reduce left ventricular hypertrophy in CKD patients [81], but total correction may not further improve LV geometry or cardiovascular outcome [82]. Besarab *et al.* randomized 1233 long-term hemodialysis patients to receive flexible dosages of epoetin alpha to achieve and maintain hematocrit values of either 42 ± 3 or 30 ± 3 % [83]. The study was stopped prematurely due to safety concerns, yet none of the other cardiovascular secondary endpoints (e.g., nonfatal myocardial infarction) reached statistical significance. The lack of effectiveness in terms of mortality reduction by increasing hemoglobin (or hematocrit) levels closer to normal was confirmed in several subsequent large clinical trials in CKD (non-ESRD) and HF patient cohorts [84, 85].

Conclusion

The prevention of HF is one of the most important treatment goals in patients with CKD. It is clear that cardiac and renal biomarkers, alone or in combination, can be used to identify individuals at heightened risk of developing HF across the spectrum of CKD. Serial monitoring of cardiovascular biomarkers, utilization of a multimarker panel, and a simple but effective HF risk score would further improve HF prediction. It is anticipated that the measurement of these biomarkers will alert physicians to asymptomatic patients at high risk who may benefit from early investigation and treatment over and above routine care. The extension of this to patients at earlier stages of CKD would create an opportunity for the earlier institution of preventive therapies, thereby decreasing the burden of disease before dialysis therapy is required. However, current guidelines do not have specific recommendations for prevention in the CKD population due to lack of adequately powered randomized controlled trials that support and validate specific therapeutic interventions.

Rather than just identifying patients at heightened risks, clinicians need strategies to lower this risk. Therefore, future investigations need to identify risk reduction strategies and, for the time being, aggressive blood pressure and volume control, smoking cessation, exercise prescription, glycemic and lipid control, and correction of severe anemia may all play a part in HF risk reduction. The use of ACE inhibitors and ARBs has demonstrated clinical benefits when indicated, but more definitive data are needed to justify routine prescription for HF prevention. In contrast, despite the potential to attenuate sympathetic overactivity and hyperaldosteronism, anti-adrenergic therapy and mineralocorticoid receptor antagonists are not commonly prescribed particularly in the ESRD population where hypotension from hemodialysis and hyperkalemia frequently occur. There is an important and urgent need for large-scale prospective trials to evaluate the use of these agents in patients with CKD for the prevention of HF.

Compliance with Ethics Guidelines

Conflict of Interest: Jennifer Kirsop and Amr Raghban have no disclosures relevant to this work. W.H. Tang received grant support from the National Institutes of Health (R01HL103931).

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ORIGINAL RESEARCH ARTICLE

Antihypertensive effects of olmesartan compared with other angiotensin receptor blockers

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Angiotensin II type 1 receptor antagonists (angiotensin receptor blockers [ARBs]) have been shown to be effective and well tolerated in hypertensive patients. Olmesartan is the seventh angiotensin receptor blocker licensed by the US Food and Drug Administration. The aim of this meta-analysis is to determine the efficacy and tolerability of olmesartan medoxomil in comparison with other ARBs.

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Introduction

Hypertension is considered to be the leading risk factor for death in the world, causing an estimated 7.5 million deaths per year (13 % of all deaths) [1]. Relationships between elevated blood pressure (BP) levels and cardiovascular disease, stroke, and renal failure have consistently been found [2]. Therefore, lowering BP is crucial in terms of prevention of end-organ damage for hypertensive patients [3].

The renin-angiotensin-aldosterone system (RAAS) is a major modulator of BP and an important therapeutic target in the treatment of hypertension [4]. By binding to the angiotensin type 1 (AT1) receptor, angiotensin II type 1 receptor antagonists (angiotensin receptor blockers [ARBs]) that inhibit RAAS have been shown to be effective and well tolerated among the different therapeutic classes of antihypertensive agents [5].

Olmesartan medoxomil is the seventh ARB licensed for the treatment of hypertension by the US Food and Drug Administration (FDA), in 2002 [6, 7]. Extensive clinical evidence has confirmed the antihypertensive efficacy and good tolerability profile of olmesartan [5]. However, the efficacy and safety of

olmesartan in comparison with other sartans (e.g., losartan and valsartan) are controversial. For example, Giles *et al* [8]. reported that olmesartan was superior to valsartan in BP control. However, Fogari *et al* [9]. reported that valsartan was more effective for BP reduction than olmesartan. No systematic reviews have been undertaken to evaluate the benefit/risk profiles of olmesartan in comparison with other ARBs.

In order to determine whether olmesartan provides better efficacy for BP control and fewer adverse events (AEs) over other ARBs, we undertook this meta-analysis of all relevant randomized controlled trials (RCTs).

Methods

Searching

Reports of RCTs of olmesartan versus other ARBs were identified through a systematic search of PubMed (up to July 2010), EMBASE (1980 to July 2010), SinoMed (up to July 2010), and the Cochrane Central Register of Controlled Trials (Cochrane Library Issue 7, 2010). The terms used for keywords and text word searching included olmesartan, ARB, losartan, valsartan, irbesartan, candesartan, eprosartan, telmisartan, atacand, teveten, avapro, cozaar, benicar, micardis, and diovan, using Boolean operators and database-specific syntax. The reference lists of original researches, reviews, letters to the editor, and case reports were also scanned to identify those not yet included in the computerized databases. The search was performed without any language restriction.

Selection

Studies meeting the following selection criteria were included in this meta-analysis: (i) study design: prospective RCTs; (ii) population: patients with hypertension, with or without other diseases such as metabolic syndrome and chronic kidney disease; (iii) interventions: olmesartan versus other ARBs, used as monotherapy; (iv) dosing regimens: titration as needed from a starting dose of monotherapy; forced titration of the therapy; parallel-group comparisons of various doses as monotherapy; (v) outcome variables: at least one of either mean seated systolic BP (SBP) or diastolic BP (DBP) reduction; mean BP reduction over 24 hours; therapeutic BP response rates and adverse events including total adverse event rate, drug-related adverse event rates, and incidence of headache, dizziness and diarrhea. The eligibility of a trial to be included in the meta-analysis was determined by two authors (WL, ZJW) independently. All work was reviewed by another author (ZZ). Only the data from the primary series were included if the same group of patients were involved in different reports in order to avoid duplication.

Validity assessment

Two authors (WL, ZJW) worked independently, using standard criteria (the adequacy of randomization, allocation concealment, blinding method, drop-out reports and follow-ups) to appraise each included article according to an adjusted quality scoring system based on the Jadad scale [10]. The quality scoring system followed was: (i) adequacy of randomization, coded as proper with detailed description of randomization (score 2), randomized but details not reported (score 1), or inappropriate randomization (score 0); (ii) allocation concealment, coded as properly used (score 2), unclear (score 1), or not used (score 0); (iii) blinding method, coded as double-blind (score 2), single-blind (score 1), or open-label or unclear (score 0); (iv) drop-outs and follow-ups, coded as data given (score 1) or data not given (score 0) [11].

Olmesartan medoxomil is the seventh ARB licensed for the treatment of hypertension by the US Food and Drug Administration (FDA) in 2002. Extensive clinical evidence has confirmed the antihypertensive efficacy and good tolerability profile of olmesartan.

Data extraction

Two of the authors (WL, ZJW) abstracted data from the identified studies independently. Disagreements were resolved by discussion. The data were extracted from each study with a predesigned review form including: the authors of the selected study; the year of publication; the location of the trial; the design of the study (whether double-blind or single-blind, parallel or crossover); the duration of the study; the number of subjects; the patients' age, sex, baseline SBP and DBP values, end-point SBP and DBP values, change from baseline in SBP and DBP, and therapeutic response rate of SBP and DBP. In addition, we retrieved the number or proportion of adverse events and withdrawals. Only the data associated with monotherapy were extracted if the patients received monotherapy followed by combination therapy if they were reported separately.

Study characteristics

We attempted to identify and include all RCTs carried out to assess the effects and tolerance associated with the use of olmesartan as compared with other ARBs in hypertensive patients.

The primary antihypertensive efficacy variables were the reduction from baseline to end of treatment in clinic DBP and SBP. A secondary efficacy variable was the therapeutic response rate of DBP (DBP <90 mmHg and/or a reduction of ≥10 mmHg). We assessed the tolerability of olmesartan by considering the overall incidence of AEs and the drug-related incidence of AEs. The incidence of three specific AEs including headache, dizziness, and diarrhea was also evaluated.

We undertook a sensitivity analysis according to the scores of quality assessment based on the Jadad scale. We reanalyzed the results after excluding the studies that scored less than 4. In addition, we conducted additional analyses including only studies published in English.

Quantitative data synthesis

Our meta-analysis was undertaken according to the Quality of Reporting Meta-analyses (QUOROM) statement [12]. Not all of the trials reported all the outcomes of interest for our analysis. Separate meta-analyses including DBP reduction, SBP reduction, BP response rate and the incidence of total, drug-related or three specific adverse events were undertaken for each comparison and outcome. We undertook a chi-squared (χ^2) test of heterogeneity and the I^2 measure of inconsistency to assess the heterogeneity between trials. The indicators were calculated with a fixed-effect mode when I^2 <50 %, indicating no significant heterogeneity. If the test for heterogeneity showed I^2 ≥50 %,

the analysis was redone with a random effects model. For continuous data, we used weighted mean difference (WMD) as effect size. For dichotomous data, we calculated the relative risk (RR) for each clinical event.

The data analysis was performed using the meta-analysis software Review Manager (Revman 5.0.2, Cochrane Collaboration, Oxford, England). When mean BP reduction and its standard deviation (SD) were not available, we computed them by using the methods given by the Cochrane handbook [13]. In addition, we created L' Abbé plots to analyze the degree of BP reduction with olmesartan in comparison with other ARBs. The scatter of the individual trials lay predominantly between the line of equality and the control axis, which suggests efficacy of olmesartan and other ARBs in BP reduction.

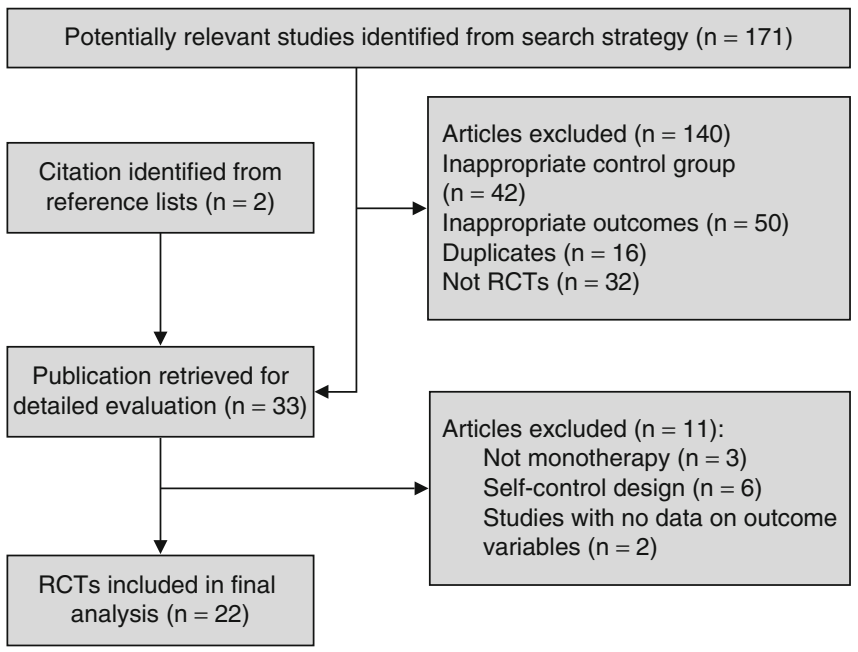

Fig. 1: Diagrammatic representation showing studies eligible for inclusion in the meta-analysis. *RCT* = randomized controlled trial.

Meta-regression

Meta-regression using STATA version 10.0 (Stata Corporation, College Station, TX, USA) was performed to determine whether specific characteristics could explain the heterogeneity among studies. We made a meta-regression to examine and test for between-group differences if the heterogeneity (I^2) was more than 75 % and more than ten trials were included. Co-variables included baseline age, sex, duration, study publication year, and DBP and SBP baseline levels. The *p*-value for explanatory variables being statistically significant was set as 0.05 [14].

Results

Trial flow

The search strategy generated 171 studies from PubMed, EMBASE, the Cochrane Library, and SinoMed. From all these studies, we identified 22 studies that met the inclusion criteria. The reasons for including the remaining 22 RCTs are listed in Figure 1.

Study characteristics

One hundred and fifty-one studies were excluded due to one of the following: inappropriate control group (*n* = 42), inappropriate outcomes (*n* = 50), duplicates (*n* = 16), not RCTs (*n* = 32), not monotherapy (*n* = 3), self-control design (*n* = 6), studies with no data on outcome variables (*n* = 2). We obtained the full text of all the 33 included relevant studies and evaluated them in detail. Twenty-two studies met the criteria for inclusion in this analysis. All the included studies used parallel designs. There were 14 double-blind trials, [6–8, 15–25] two single-blind trials, [26, 27] two open-label trials, [9, 28] and four trials not mentioning the blinding methods [29–32]. Seven studies were multicenter RCTs, [7, 8, 15, 17, 20, 24, 25] one was not clear, [27] while the others were single-centered. [6, 9, 16–19, 21–23, 26, 28–32] All the trials were described as randomized and only one trial [27] reported the generation of randomization. None mentioned allocation concealment. Ten trials [6, 7, 15, 19, 20, 23, 26, 30, 31, 32] used elective titration of the dose; one [18] used forced titration dose and 11 trials [8, 9, 16, 17, 21, 24, 25, 27–30] used no titration dose. All the trials reported the follow-up time, ranging from 2 weeks to 24 weeks, but one trial lasted 12 months [27]. Of all the studies, olmesartan was compared with losartan in 13 trials and with valsartan in nine trials. Both losartan and valsartan appeared in three studies [8, 17, 18]. We carried out a descriptive analysis of candesartan (three trials) or irbesartan (one trial) as there were insufficient data to undertake a meta-analysis. Both candesartan and irbesartan appeared in one trial [17]. Specific characteristics of each included article are listed in Table I.

Dose regimen

In our meta-analysis, the following doses were included: olmesartan 20 and and 20–40 mg, losartan 50 and 50–100 mg, valsartan 80 and 160 mg, candesartan 8 mg, and irbesartan 150 mg. Evaluated doses were all recommended in US, Japanese, and European product labels. Conlin *et al.* [33] compared the antihypertensive efficacy of losartan, valsartan, irbesartan, and candesartan in 2000. In that meta-analysis, the authors concluded that at recommended doses the four ARBs showed a near-flat dose response curve that suggested that monotherapy dose titration offered limited benefit [33]. In our meta-analysis, we combined fixed dose and dose titration into the same group.

Olmesartan versus losartan

Efficacy

Twelve trials involving 2133 patients compared olmesartan with losartan in clinic BP reduction. There was a significant difference that favored olmesartan in DBP and SBP (DBP: WMD 1.61; 95 % confidence interval [CI] 0.59, 2.62; random effects model, Figure 2; SBP: WMD 3.19; 95 % CI 0.46, 5.92; random effects model, Figure 3). There were seven trials [6, 7, 15, 19, 22, 26, 31] involving 860 patients in response rate, and no significant difference was found between the two arms (RR 1.01; 95 % CI 0.95, 1.07).

Tolerability

Ten trials were evaluated for the total incidence of adverse events with olmesartan compared with losartan. There was no

Table I: Characteristics of RCTs included in the meta-analysis.

Study and year	Design	No. of patients	Mean age, y	Sex, *n* (male/female)	Study center	Duration of study	Diagnosis	Quality grade
Chen *et al.* 2007[31]	NC	121	55	70/51	Single-center	8 wk	Mild-to-moderate hypertension	3
Giles & Oparil 2005[18]	DB-P	617	NC	NC	Single-center	8 wk	Mild-to-moderate hypertension	4
Giles *et al.* 2007[8]	DB-P	598	52	376/222	Multicenter	2 wk	Essential hypertension	4
He *et al.* 2008[16]	DB-P	128	50	64/64	Single-center	8 wk	Mild-to-moderate hypertension	5
He *et al.* 2007[26]	SB-P	68	58	32/36	Single-center	8 wk	Mild-to-moderate hypertension	3
Hu *et al.* 2009[15]	DB-P	237	50	NC	Multicenter	8 wk	Mild-to-moderate hypertension	4
Jing *et al.* 2006[7]	DB -P	221	53	121/100	Multicenter	8 wk	Mild-to-moderate hypertension	4
Kong *et al.* 2008[19]	DB-P	40	56	18/22	Single-center	8 wk	Mild-to-moderate hypertension	5
Liu 2009[22]	DB-P	136	NC	NC	Single-center	8 wk	Mild-to-moderate hypertension	4
Oparil *et al.* 2001[17]	DB-P	588	52	365/223	Multicenter	8 wk	Mild-to-moderate hypertension	4
Xi & Tian 2009[23]	DB-P	60	73	42/18	Single-center	8 wk	Isolated systolic hypertension	4
Zhang *et al.* 2006[6]	DB-P	40	48	26/14	Single-center	8 wk	Mild-to-moderate hypertension	4
Destro *et al.* 2005[28]	OP-P	114	NC	64/50	Single-center	8 wk	Mild-to-moderate hypertension	3
Fogari *et al.* 2006[9]	OP-P	130	60	NC	Single-center	4 wk	Mild-to-moderate hypertension	2
Hao *et al.* 2010[21]	DB-P	54	53	38/16	Single-center	24 wk	Mild-to-moderate hypertension	4
Li *et al.* 2008[29]	NC	80	49	62/18	Single-center	8 wk	Mild-to-moderate hypertension	3
Li *et al.* 2009[30]	NC	90	48	75/15	Single-center	8 wk	Mild-to-moderate hypertension	3
Zhang *et al.* 2008[32]	NC	64	55	18/16	Single-center	8 wk	Mild-to-moderate hypertension	3
Zhu *et al.* 2006[20]	DB-P	287	54	182/98	Multicenter	8 wk	Mild-to-moderate hypertension	4
Tsutamoto *et al.* 2009[27]	SB-P	50	68	31/19	NC	12mo	Essential hypertension	4
Brunner & Arakawa 2006[24]	DB-P	635	52	359/276	Multicenter	8 wk	Mild-to-moderate hypertension	5
Smith *et al.* 2005[25]	DB-P	534	52	326/208	Multicenter	8 wk	Essential hypertension	4

DB-P = double-blind parallel; *NC*= not clear; *OP-P* = open-label parallel; *RCT*= randomized controlled trial; *SB-P* = single-blind parallel.

significant difference between the two groups (RR 0.98; 95 % CI 0.83, 1.15; Figure 4). There was also no significant difference in the incidence of drug-related AEs, headache, dizziness, and diarrhea between the two groups (Table II).

Meta-regression

Twelve trials were involved and the heterogeneity (I^2) was more than 75 % in the meta-analysis of SBP reduction between olmesartan and losartan. We undertook a meta-regression according to study design to determine whether specific characteristics could explain the heterogeneity. The relative meta-regression analysis showed that the patients' age and sex, duration of the study, number of patients included, publication year of the studies (table III), and BP baseline (Figure 5) did not contribute to the heterogeneity.

Sensitivity analysis

We reanalyzed the results after excluding the studies that scored less than 4 (table I). A significant difference that favored olmesartan still existed in DBP reduction (WMD 1.73; 95 % CI 0.58, 2.88; random effects model). However, no significant difference was found in SBP reduction between the two arms (WMD 2.83; 95 % CI −0.23, 5.89; random effects model). We also reanalyzed the results after the exclusion of non-English studies. A significant difference that favored olmesartan was found in both DBP and SBP reduction (DBP: WMD 3.06; 95 % CI 2.39, 3.74; SBP: WMD 3.66; 95 % CI 2.22, 5.09; fixed-effect model).

Olmesartan versus valsartan

Efficacy

Nine trials involving 1595 patients compared olmesartan with valsartan in clinic BP reduction. There was a significant difference that favored olmesartan in SBP (WMD 1.72; 95 % CI 0.29, 3.16; random effects model, Figure 3). However, no significant difference was found in DBP reduction between the two arms (WMD 0.65; 95 % CI −0.93, 2.22; random effects model, Figure 2). There were three trials [6, 29, 30] involving 228 patients in response rate, and no significant difference

Table II: All-cause and drug-related adverse events, headache, dizziness, and diarrhea with olmesartan vs losartan and valsartan.

Interventions	Adverse events (all-cause)		Adverse events (drug-related)		Headache		Dizziness		Diarrhea	
	RR	95 % CI	RR	95 % CI	RR	95 % CI	RR	95 % CI	RR	95 % CI
Olmesartan vs losartan	0.98	0.83, 1.15	0.92	0.62, 1.36	1.07	0.66, 1.74	1.16	0.56, 2.38	1.51	0.54, 4.18
Olmesartan vs valsartan	0.86	0.74, 1.01	0.96	0.65, 1.43	1.35	0.82, 2.24	1.38	0.62, 3.05	0.60	0.25, 1.43

CI = confidence interval; *RR*= relative risk.

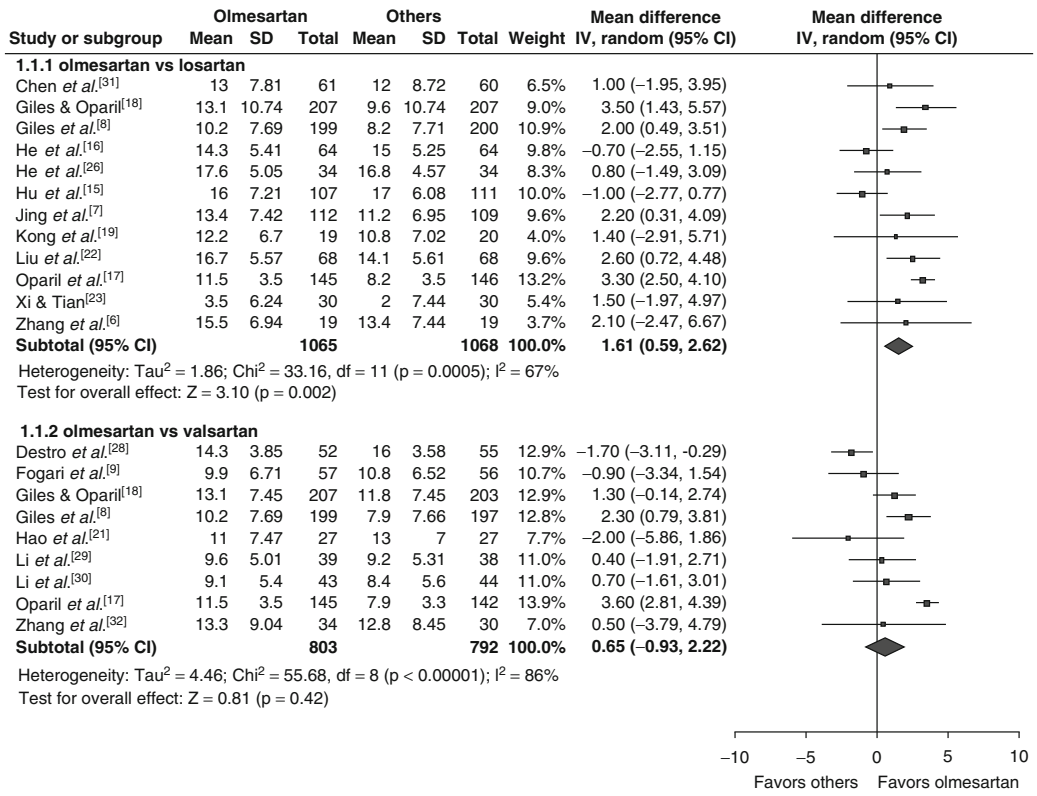

Fig. 2: Diastolic blood pressure reduction with olmesartan compared with losartan or valsartan. *CI* = confidence interval; *df* = degrees of freedom; *IV* = inverse variance.

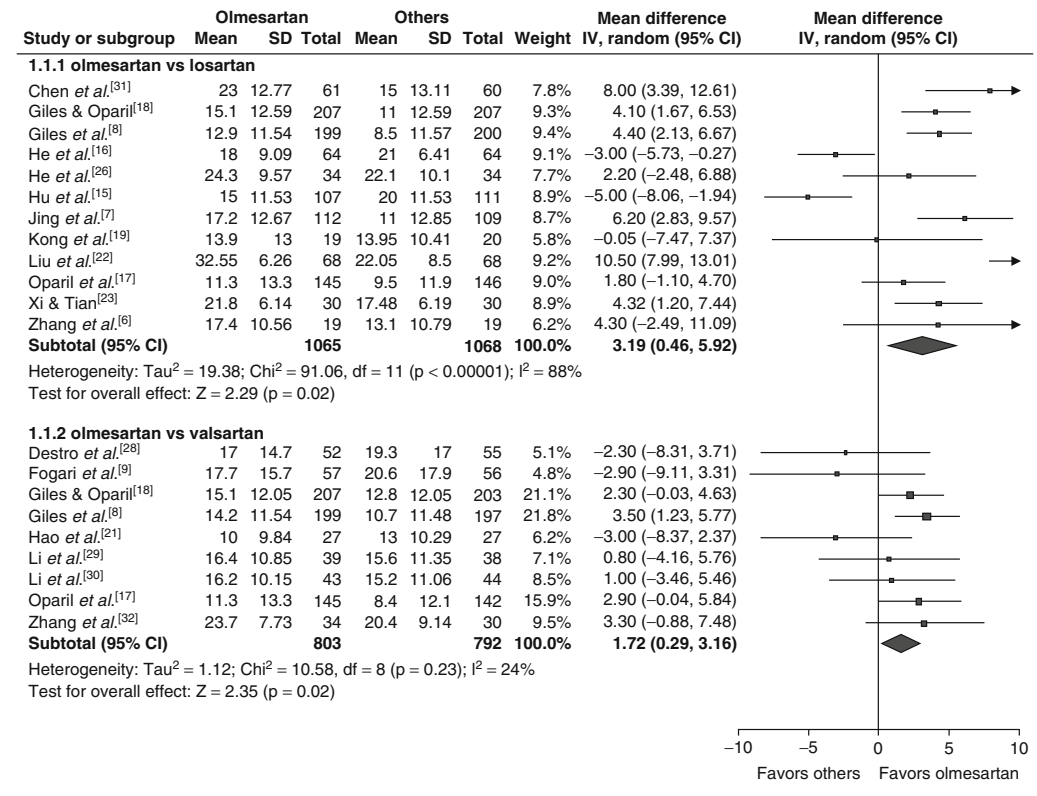

Fig. 3: Systolic blood pressure reduction with olmesartan compared with losartan or valsartan. *CI* = confidence interval; *df* = degrees of freedom; *IV* = inverse variance.

was found between the two arms (RR 1.02; 95 % CI 0.92, 1.13).

Tolerability

Six trials evaluated the total incidence of adverse events of olmesartan compared with valsartan. There was no significant difference between the two groups (RR 0.86; 95 % CI 0.74, 1.01; Figure 4). There was also no significant difference in the incidence of drug-related AEs, headache, dizziness, and diarrhea between the two groups (table II).

Sensitivity analysis

We reanalyzed the results after excluding the studies with low scores (<4) according to table I. A significant difference that favored olmesartan was found in SBP reduction (WMD 2.53; 95 % CI 1.15, 3.90; fixed-effect model). We also found a significant difference that favored olmesartan in DBP reduction (WMD 1.92; 95 % CI 0.24, 3.59; random effects model). In addition, we reanalyzed the results after the exclusion of non-English studies. There was still a significant difference that favored olmesartan in SBP reduction (WMD 2.37; 95 % CI 1.02, 3.73; fixed-effect model). No significant difference was found in DBP reduction (WMD 1.01; 95 % CI –1.14, 3.16; random effects model).

Olmesartan was superior to candesartan in mean BP reduction over 24 hours. In addition, olmesartan demonstrated greater reductions in both DBP and SBP during the last 4 and 2 hours of the dosing interval.

Olmesartan versus candesartan or irbesartan

There was no significant difference in BP change between olmesartan and candesartan [27]. Olmesartan was superior to candesartan in mean BP reduction over 24 hours [24]. In addition, olmesartan demonstrated greater reductions in both DBP and SBP during the last 4 and 2 hours of the dosing interval [24]. Olmesartan produced a greater reduction in DBP, and a numerically greater but not statistically different SBP change was found in comparison with irbesartan [17]. Moreover, the magnitude of BP lowering with olmesartan was numerically greater than that with irbesartan over 24 hours without statistical significance [17, 25]. No significant difference in total adverse events was found between olmesartan and candesartan [24] or irbesartan [17, 25].

L'Abbé plots

Of all the studies, the detailed efficacy of DBP and SBP reduction between olmesartan and other ARBs (losartan, valsartan, candesartan, irbesartan) was presented in L'Abbé plots (Figure 6). Seventy-seven percent of trials (17 of 22) lay under the line of equality in DBP reduction analysis. Seventy-three percent of trials (11 of 15) lay under the line of

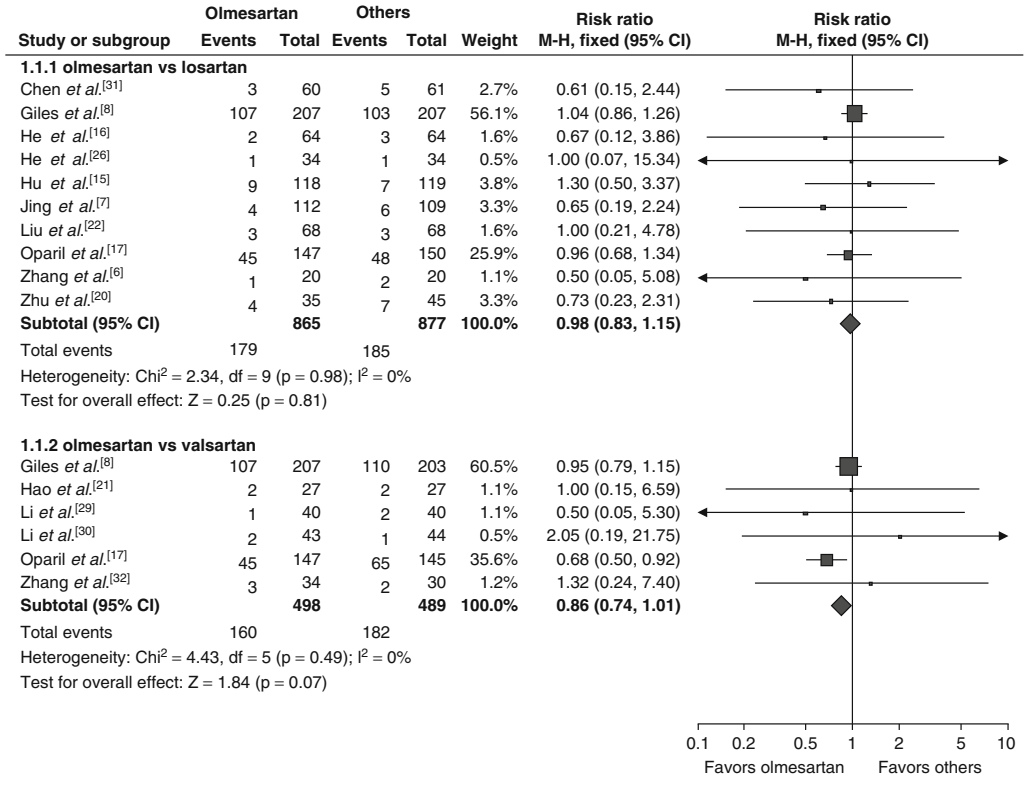

Fig. 4: Total incidence of adverse events with olmesartan compared with losartan or valsartan. *CI* = confidence interval; *df* = degrees of freedom; *MH* = Mantel-Haenzel.

equality in SBP reduction analysis. Therefore, olmesartan was shown to provide better efficacy compared with other ARBs.

Discussion

Our meta-analysis examined the efficacy and tolerability of olmesartan, losartan, valsartan, candesartan, and irbesartan when administered at their recommended doses. Findings from this meta-analysis of 22 RCTs revealed that olmesartan provided superior BP-lowering efficacy compared with other ARBs. The evidence was sufficient to determine the better efficacy in SBP reduction when olmesartan was compared with losartan or valsartan. Available data indicated that olmesartan was more effective than losartan but as effective as valsartan in DBP reduction. ARBs are well known for having a placebo-like tolerability profile at all recommended dosages [34]. Olmesartan did not differ from losartan or valsartan with regard to the total incidence of adverse events. As indicated by the L'Abbé plots, most trials showed that olmesartan provided better efficacy compared with other ARBs (losartan, valsartan, candesartan, and irbesartan) in BP reduction. These effects can be partially explained by the substantially longer half-life of olmesartan than that of losartan or valsartan, since a longer half-life is associated with a longer duration of action [17].

RAAS is an important mediator in the pathophysiology of hypertension. The excessive activity in the RAAS plays a key role in target end-organ damage, such as congestive heart failure, myocardial infarction, coronary artery disease, and end-stage renal disease [5]. Although there are other angiotensin peptides with biologic effects, angiotensin II is the major end-product of the system [35]. ARBs including olmesartan block the RAAS through the angiotensin (AT)1 receptor, effectively inhibiting the vasoconstrictor and aldosterone-secreting effects of angiotensin II [5]. Nevertheless, it is still unclear which ARB is preferred in clinical use [36]. It is necessary to determine which ARB is the best agent with a better efficacy for BP control and smaller incidence of adverse events. We undertook this meta-analysis to evaluate the efficacy and tolerability of olmesartan compared with other ARBs. However, we did not include eprosartan or telmisartan in the analyses due to a lack of RCTs with appropriate outcomes.

Previously, one review had evaluated the available literature qualitatively to determine whether all ARBs have equivalent efficacy and tolerability in the treatment of hypertensive patients [5]. Olmesartan provided better antihypertensive efficacy than losartan, valsartan, candesartan, and irbesartan in that review. Several RCTs have also evaluated the antihypertensive efficacy of olmesartan compared with other ARBs. However, our meta-analysis, which combines data across studies to make a quantitative evaluation, had more robust evidence for supporting that conclusion. A previous meta-analysis that compared valsartan with other ARBs in the treatment of hypertension [37] reported that valsartan and olmesartan demonstrated comparable efficacy across dosing ranges. However, five more RCTs were included in our meta-analysis for a total of 803 patients. Our results showed that olmesartan provided better antihypertensive efficacy in SBP reduction.

Our meta-analysis is the first to focus on the superiority of olmesartan over other ARBs with regard to efficacy and tolerability. We used a wide range of clinically relevant variables to evaluate the efficacy and

Table III: Meta-regression analysis by study characteristics.

Characteristic	No.	*p*-Value
Mean age, y		0.936
≤55	8	
>55	3	
Sex (m/f)		0.434
≤1	3	
>1	6	
Number		0.65
≤100	4	
>100	7	
Duration, wk		0.051
8	10	
<8	1	
Study year		0.621
≤2005	10	
>2005	1	

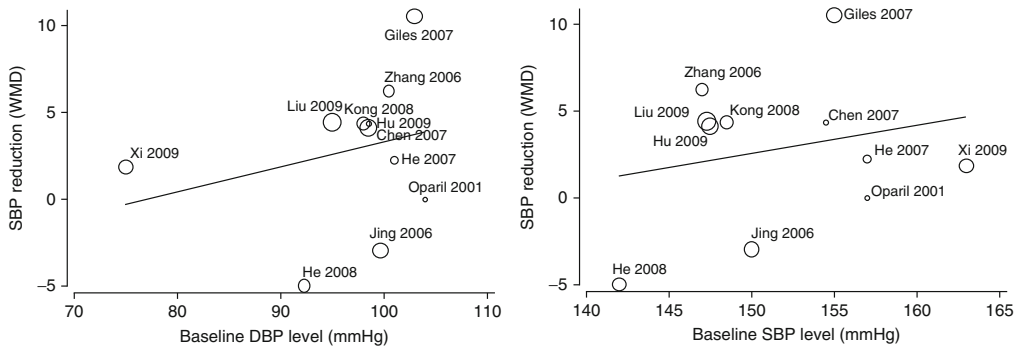

Fig. 5: Meta-regression plots of systolic blood pressure (SBP) reduction differences vs baseline blood pressure (BP) level. Circles represent the estimate from each study, sized according to the precision of each estimate. Fitted dashed lines represent the summary meta-regressions for SBP reduction outcome. The relationship showed no statistical significance for either SBP ($p = 0.571$) or diastolic BP (DBP) [$p = 0.444$]. See Table I for reference citations. *WMD* = weighted mean difference.

tolerability of its BP reduction. In addition, we undertook L'Abbé plots to evaluate the efficacy visually. For the factors that could potentially influence the results and generate heterogeneity such as patients' age and sex, duration of study, number of patients, and baseline BP, we performed a meta-regression to examine whether these specific baseline characteristics could explain the heterogeneity among studies.

Our meta-analysis also has some limitations. Due to the lack of head-to-head RCTs, it was difficult to perform a meta-analysis to evaluate the efficacy and tolerability of olmesartan compared with irbesartan or candesartan. Only a small number of RCTs had investigated the ability of ARBs to control 24-hour BP, therefore we could not undertake a meta-analysis of 24-hour BP lowering, especially early morning change, which has been shown to be associated with increased rates of cardiovascular events [25]. The quality of the studies also varied. Some of the included studies were poorly reported, with seven trials scoring less than 4 on the adjusted Jadad score system. Dose regimens also varied.

Pragmatic well-designed RCTs for future research are required. Specifically, further well-designed RCTs should include larger sample sizes and focus on more secondary endpoints such as 24-hour BP control, cardiac-cerebrovascular events, and adverse events. In particular, it seems important to determine how well olmesartan works in patients who fail to respond adequately to other sartans, and whether olmesartan is associated with the long-term reduction of cardiovascular disease morbidity and mortality. More studies should be conducted to determine the differences between olmesartan and other ARBs besides losartan or valsartan.

Our meta-analysis examined the efficacy and tolerability of olmesartan, losartan, valsartan, candesartan, and irbesartan when administered at their recommended doses. Findings from this meta-analysis of 22 RCTs revealed that olmesartan provided superior BP-lowering efficacy compared with other ARBs.

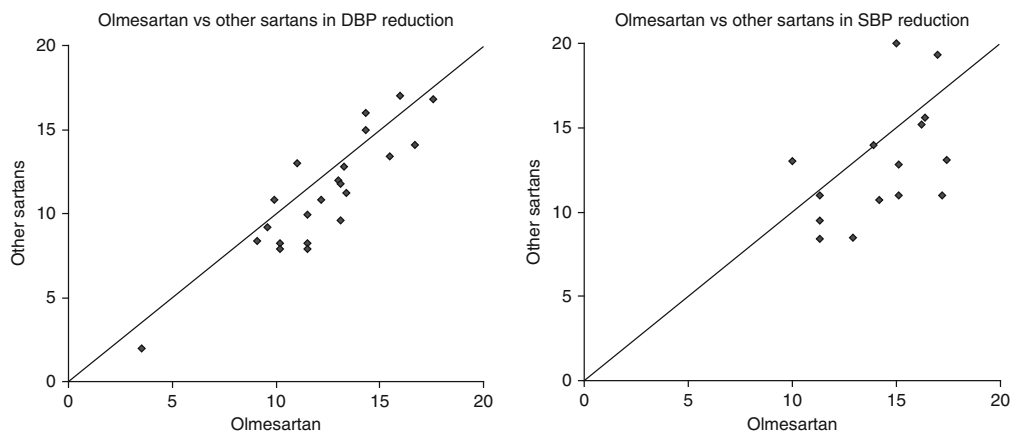

Fig. 6: Olmesartan vs other sartans in diastolic blood pressure (DBP) and systolic blood pressure (SBP) reduction. For references see Table I.

Conclusion

Olmesartan provides better antihypertensive efficacy in comparison with losartan and valsartan. With regard to the incidence of adverse events, olmesartan shows similar tolerability compared with other ARBs (losartan, valsartan, candesartan, and irbesartan). Therefore, olmesartan is a suitable treatment choice for controlling high BP.

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Drs Long Wang and Jian-wei Zhao contributed equally to this work.

Conflicts of interest: The authors have no conflicts of interest directly relevant to this study.

References available on request

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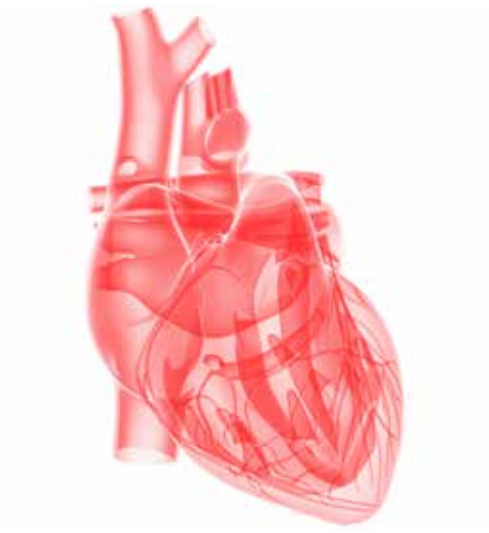
Source: Long Wang, Jian-wei Zhao, Bing Liu, et al. Antihypertensive effects of olmesartan compared with other angiotensin receptor blockers: a meta-analysis. Am J Cardiovasc Drugs 2012; 12(5): 335–344. DOI 1175-3277/12/0005-0335/$49.95/0.

Inferior vena cava diameter in acute decompensated heart failure as predictor of all-cause mortality

Inferior vena cava (IVC) diameter can be used to approximate right atrial pressure in patients admitted for acute decompensated heart failure (ADHF). Recent studies linked IVC dilation to an increased risk of early re-admission and short-term mortality. Moreover, renal insufficiency (RI) is an established risk factor for mortality in ADHF and is associated with congestion. We hypothesized that the IVC diameter is a marker of all-cause mortality but its prognostic impact may be influenced by kidney function. We analyzed data of 1101 patients admitted for ADHF with available echocardiography of the IVC by chart review and death registry linkage. Patients were dichotomized according to a cut-off value of 21 mm. Cox proportional hazards model was used to identify mortality predictors. A dilated IVC was detected in 474 (43.1 %)



patients. Overall, 400 (36.3 %) patients died within 3 years. All-cause mortality was significantly higher in patients with dilated IVC [hazard ratio 1.45 (confidence interval 1.21–1.74); $p < 0.001$]. However, a dilated IVC was only associated with all-cause mortality in patients with RI function [hazard ratio 1.60 (confidence interval 1.26–2.03); $p < 0.001$] but not in patients with a preserved kidney function [hazard ratio 1.04 (confidence interval 0.72–1.50); $P = 0.84$]. IVC diameter was identified as an independent predictor for all-cause mortality in a Cox proportional hazards model with a significant interaction between IVC diameter and baseline kidney function. In conclusion, IVC dilation is a marker of high mortality risk in patients admitted for ADHF. However, this observation was confined to patients with RI.

Source: Alexander Jobs, Kerstin Brünjes, Alexander Katalinic, et al. Inferior vena cava diameter in acute decompensated heart failure as predictor of all-cause mortality. Heart and Vessels 2017; 32(7): 856–864. DOI 10.1007/s00380-017-0944-0. © Springer Japan 2017.

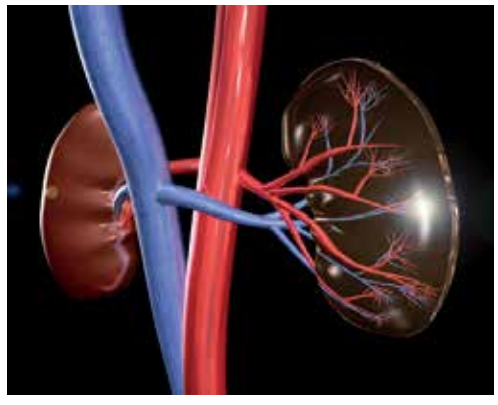
The cost-effectiveness of using chronic kidney disease risk scores to screen for early-stage chronic kidney disease

Better treatment during early stages of chronic kidney disease (CKD) may slow progression to end-stage renal disease and decrease associated complications and medical costs. Achieving early treatment of CKD is challenging, however, because a large fraction of persons with CKD are unaware of having this disease. Screening for CKD is one important method for increasing awareness. We examined the cost-effectiveness of identifying persons for early-stage CKD screening (i.e., screening for moderate albuminuria) using published CKD risk scores.

We used the CKD Health Policy Model, a micro-simulation model, to simulate the cost-effectiveness of using CKD two published risk scores by Bang *et al.* and Kshirsagar *et al.* to identify persons in the US for CKD screening with testing for albuminuria. Alternative risk score thresholds were tested (0.20, 0.15, 0.10, 0.05, and 0.02) above which persons were assigned to receive screening at alternative intervals (1-, 2-, and 5-year) for follow-up screening if the first screening was negative. We examined incremental cost-effectiveness ratios (ICERs), incremental lifetime costs divided by incremental lifetime QALYs, relative to the next higher screening threshold to assess cost-effectiveness. Cost-effective scenarios were determined as those with ICERs less than $50,000 per QALY. Among the cost-effective scenarios, the optimal scenario was determined as the one that resulted in the highest lifetime QALYs.

ICERs ranged from $8,823 per QALY to $124,626 per QALY for the Bang *et al.* risk score and $6,342 per QALY to $405,861 per QALY for the Kshirsagar *et al.* risk score. The Bang *et al.* risk score with a threshold of 0.02 and 2-year follow-up screening was found to be optimal because it had an ICER less than $50,000 per QALY and resulted in the highest lifetime QALYs.

This study indicates that using these CKD risk scores may allow clinicians to cost-effectively identify a broader population for CKD screening with testing for albuminuria and

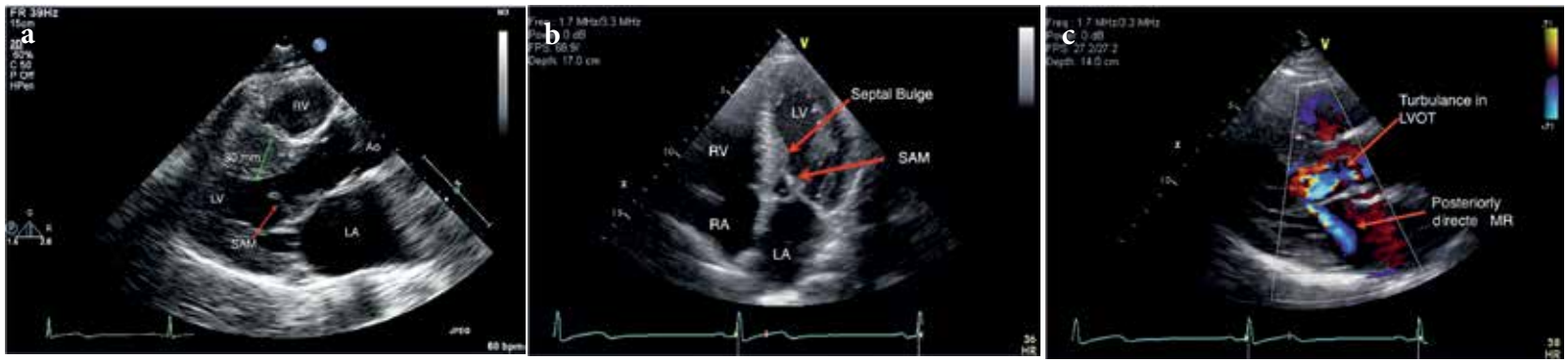


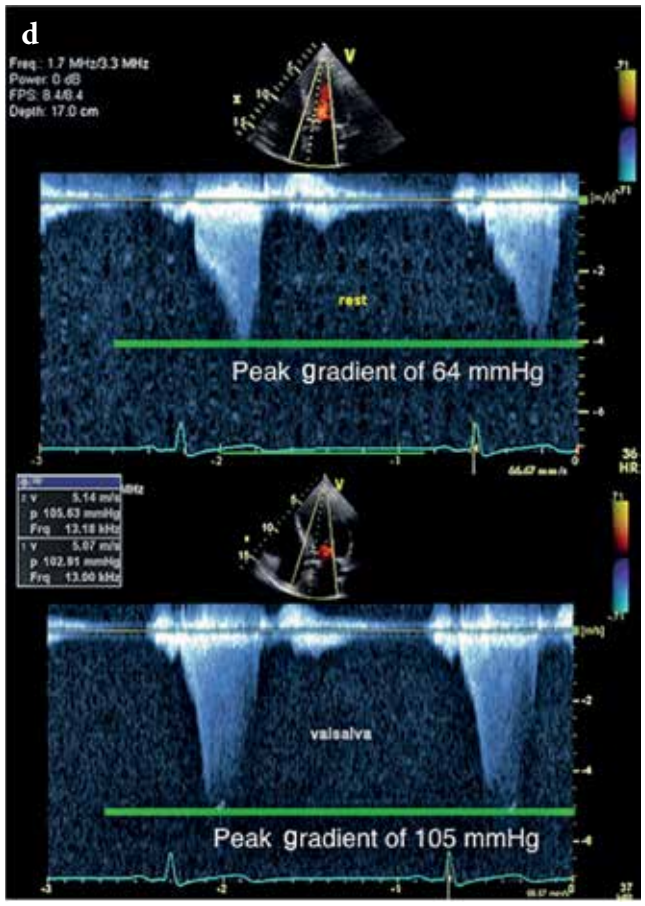
potentially detect people with CKD at earlier stages of the disease than current approaches of screening only persons with diabetes or hypertension.

Source: Benjamin O. Yarnoff, Thomas J. Hoerger, Siobhan K. Simpson, et al. The cost-effectiveness of using chronic kidney disease risk scores to screen for early-stage chronic kidney disease. BMC Nephrol 2017; 18:85. DOI 10.1186/s12882-017-0497-6. © The Author(s). 2017.

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is a complex disorder with both genetic and sporadic forms that differ in presentation but all have an inappropriate level of left ventricular hypertrophy. HCM can be defined by left ventricular hypertrophy of >15 mm in absence of other systemic cause. Other characteristics of HCM include diastolic dysfunction, dynamic ventricular outflow obstruction, progression to systolic dysfunction, and increased risk for ventricular arrhythmias.





(**a**) Parasternal long axis view recorded in a patient with hypertrophic cardiomyopathy. There is septal hypertrophy, left ventricular hypertrophy, as well as visualization of the systolic anterior motion (*SAM*) of the mitral valve leaflet. *LV* Left Ventricle, *RV* Right Ventricle, *RA* Right Atrium, *Ao* Aorta, *LA* Left Atrium. (**b**) Apical four-chamber view in a patient with hypertrophic cardiomyopathy. Features include midventricular septal hypertrophy and a bulge with systolic anterior motion of mitral valve without flow obstruction. *LV* Left Ventricle, *RV* Right Ventricle, *RA* Right Atrium, *SAM* Systolic Anterior Movement, *LA* Left Atrium. (**c**) Parasternal long axis view with color Doppler imaging in an individual with hypertrophic cardiomyopathy. Systolic anterior motion of the mitral valve leads to turbulent flow in the left ventricular outflow tract (*LVOT*). This also creates secondary mitral regurgitation with a posteriorly directed jet as shown. (**d**) Continuous Doppler of left ventricular outflow tract to evaluate quantification of outflow tract obstruction in an individual with hypertrophic cardiomyopathy. It shows characteristic increased late-peaking outflow gradient at rest above with subsequent increase with Valsalva (decreased preload).

Source: Carrie Puckett, Michael Shapiro, Sarah J. Goodlin. Congestive heart failure. In: Giuseppe Guglielmi, Wilfred C. G. Peh, Ali Guermazi (eds). Geriatric Imaging. 1st ed. Berlin: Springer-Verlag; 2013, pp 235–257. DOI 10.1007/978-3-642-35579-0_11. © Springer-Verlag Berlin Heidelberg 2013.

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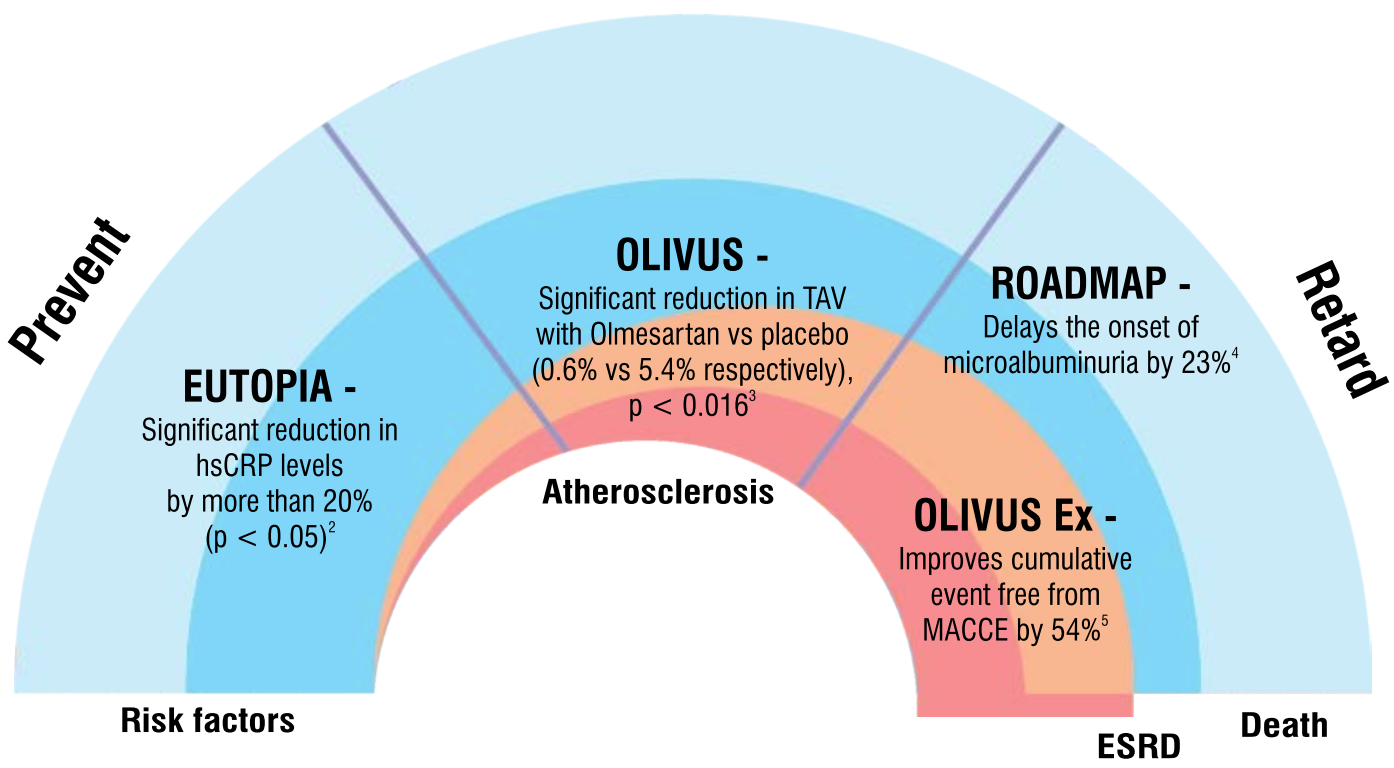

TAV – Total Atheroma Volume, MACCE - Major Adverse Cardio- and Cerebrovascular Events

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