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How to measure 24 hour central blood pressure and its potential clinical implications

The evaluation of 24 hour central blood pressure (24 h cBP) combines the cBP non-invasive assessment with the 24 h ambulatory BP measurement. The major strength of the 24 h cBP evaluation is the ability to assess the degree of circadian changes between central and peripheral BP, namely, 24 h BP amplification. This allows an accurate quantification of the degree of spatial and temporal BP variability in each single individual. BP amplification depends from a number of factors, such as the interaction between pressure and flow pulsatile motions, vasomotor tone, arterial tapering and other physiological and anthropometrical determinants. The assessment of 24 h BP amplification, a relatively pressure-independent parameter, may be helpful in better refining the risk of organ damage and future CV events over traditional measures of office and 24 h brachial BP. Currently, only few devices enable the assessment of 24 h cBP. These devices are based on peripheral (brachial or radial) BP waveform detection, and reconstruction of central BP waveform through mathematical models. The estimation of 24 h cBP imputed from multivariate regression equations was also proposed. Clinical data are still scarce and, although suggesting a possible superiority of 24 h cBP over brachial BP in the association with markers of organ damage, they are limited by methodological and technical aspects. There is an urgent need of a standardized methodology and rigorous validation protocols for the 24 h cBP assessment. The field of 24 h cBP measurement still requires significant advancements of scientific knowledge before its introduction into clinical practice.

Source: Giacomo Pucci, Francesca Battista, Alessandra Crocetti, Giovanni Tilocca, Enrico Boschetti. How to measure 24 hour central blood pressure and its potential clinical implications. High Blood Press Cardiovasc Prev. 2017; 24(2):141–148. DOI: 10.1007/s40292-017-0202-7. © Springer International Publishing Switzerland 2017.

Subclinical markers of cardiovascular disease predict adverse outcomes in chronic kidney disease patients with normal left ventricular ejection fraction

Emerging cardiovascular biomarkers, such as speckle tracking echocardiography (STE) and aortic pulse wave velocity (aPWV), have recently demonstrated the presence of subclinical left ventricular dysfunction and arterial stiffening in patients with chronic kidney disease (CKD) and no previous cardiovascular history. However, limited information exists on the prognostic impact of these biomarkers. We aimed to investigate whether STE and aPWV predict major adverse cardiac events (MACE) in this patient population. In this cohort study, we prospectively analysed 106 CKD patients with no overt cardiovascular disease (CVD) and normal left ventricular ejection fraction. Cardiac deformation was measured using STE while aPWV was measured using arterial tonometry. The primary end-point was the composite of all-cause mortality, acute coronary syndrome, stable angina requiring revascularization (either using percutaneous coronary intervention or coronary artery bypass surgery), hospitalization for heart failure and stroke. Over a median follow-up period of 49 months (interquartile range 11–63 months), 26 patients (24.5 %) reached the primary endpoint. In a multivariable Cox hazards model, global longitudinal strain (GLS) (HR 1.12, 95 % CI 1.02–1.29, $p = 0.041$) and aPWV (HR 1.31, 95 % CI 1.05–1.41, $p = 0.021$) were significant, independent predictors of MACE. GLS and aPWV independently predict MACE in CKD patients with normal EF and no clinically overt CVD.

Source: Samir Sulemane, Vasileios F. Panoulas, Athanasios Bratsas, Julia Grapsa, Edwina A. Brown, Petros Nihoyannopoulos. Subclinical markers of cardiovascular disease predict adverse outcomes in chronic kidney disease patients with normal left ventricular ejection fraction. Int J Cardiovasc Imaging. 2017; 33(5): 687–698. DOI: 10.1007/s10554-016-1059-x. © The Author(s) 2017.

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Strategies and cost-effectiveness evaluation of persistent albuminuria screening among high-risk population of chronic kidney disease

Screening for persistent albuminuria among the high-risk population is important for early detection of CKD while studies regarding screening protocol and related cost-effectiveness analysis are limited. This study explored a feasible and cost-efficient screening strategy for detecting persistent albuminuria among the high-risk population.

A cohort study including 157 clinically stable outpatients with a risk factor of CKD and whose laboratory tests revealed an albumin-creatinine-ratio (ACR) between 30 and 300 mg/g of creatinine during the previous 12 months was conducted to assess the validity of alternative screening strategies. Each participant collected three first morning urine samples in three consecutive months. These samples were labeled as DAY-1, MONTH-2 and MONTH-3. In the first month, a random spot sample in the afternoon of the first day and another morning sample on the second day were collected and labeled as Random and DAY-2. Persistent albuminuria was defined by abnormal ACR (≥30 mg/g creatinine) for DAY-1, MONTH-2 and MONTH-3. Alternative strategies were DAY-1; Random; DAY-1 + Random; DAY-1 + DAY-2; and DAY-1 + Random + DAY-2. To evaluate the economic performance of those alternative strategies, a hybrid decision tree/Markov model was developed based on the cohort study to simulate both clinical and cost-effectiveness outcomes. Sensitivity analyses were conducted to investigate assumptions of the model and to examine the model's robustness.

Altogether, 82 patients exhibited persistent albuminuria. All of the five strategies had sensitivity higher than 90 %. Of these strategies, Random had the lowest specificity (46.7 %), and DAY-1 + Random + DAY-2 had the highest specificity (81.3 %). Estimated cost for each quality adjusted life year (QALYs) gained were ¥112,335.88 for DAY-1 + Random, ¥8134.69 for Random and ¥10,327.99 for DAY-1 + Random + DAY-2. When compared with DAY-1 strategy, the sensitivity and specificity of which were 100.0 and 69.3 %, respectively. DAY-1 + Random + DAY-2 had the highest effectiveness and incremental effectiveness of 11.87 and 0.73 QALYs. At a willingness-to-pay threshold of ¥100,000 per QALY, DAY-1 + Random + DAY-2 had the highest acceptability of 91.0 %. Sensitivity analyses demonstrated the robustness of the results.

In order to make a quick diagnosis of persistent albuminuria among high-risk population, the strategy of combining two first morning urine samples and one randomized spot urine sample in two consecutive days is accurate, saves time, and is cost-effective.

Source: Huaiyu Wang, Li Yang, Fang Wang, Luxia Zhang. Strategies and cost-effectiveness evaluation of persistent albuminuria screening among high-risk population of chronic kidney disease. BMC Nephrol. 2017; 18:135. DOI: 10.1186/s12882-017-0538-1. © The Author(s). 2017.

Echocardiographic correlates of left ventricular filling pressures and acute cardio-renal syndrome in ST segment elevation myocardial infarction patients

Increased transmitral flow velocity (*E*) to the early mitral annulus velocity (*e′*) ratio (*E/e′*), signifying increased cardiac filling pressure, was previously found to be associated with deterioration of renal function in patients with congestive heart failure. No study, however, included patients with acute myocardial ischemia. We hypothesized that elevated *E/e′* ratio would be associated with an increased risk of acute kidney injury (AKI) in ST elevation myocardial infarction (STEMI) patients undergoing primary percutaneous coronary intervention (PCI).

We conducted a retrospective study of 804 consecutive STEMI patients between June 2012 and December 2015 who underwent primary PCI and had a comprehensive echocardiographic examination performed within 72 h of hospital admission. Patients were stratified according to *E/e′* ratio above and ≤ 15, and assessed for AKI using the KDIGO criteria, defined as either a serum creatinine rise > 0.3 mg/dl, or an increase in serum creatinine ≥ 1.5 times baseline.

Patients with *E/e′* ratio >15 had lower left ventricular (LV) ejection fraction, higher systolic pulmonary artery pressures, as well as right atrial pressures, and demonstrated worse in-hospital outcomes. Patients with *E/e′* ratio > 15 had more AKI complicating STEMI (27 vs. 7 %; $p < 0.001$). In multivariate logistic regression model, *E/e′* ratio > 15 was independently associated with AKI (OR = 1.87, 95 % CI 0.99–3.52; $p = 0.05$). Other variables associated with AKI included diabetes, LV ejection fraction, and glomerular filtration rate.

Among STEMI patients undergoing primary PCI, the early *E/e′* ratio > 15 was associated with increased risk for AKI.

Source: Nir Flint, Natalia Kaufman, Amir Gal-Oz, et al. Echocardiographic correlates of left ventricular filling pressures and acute cardio-renal syndrome in ST segment elevation myocardial infarction patients. Clin Res Cardiol. 2017; 106(2): 120–126. DOI: 10.1007/s00392-016-1031-8. © Springer-Verlag Berlin Heidelberg 2016.

EPIDEMIOLOGY OF HEART FAILURE

Epidemiology and importance of renal dysfunction in heart failure patients

Gregory Giamouzis, Andreas P. Kalogeropoulos, Javed Butler, *et al.*

The development of renal dysfunction (RD) or worsening renal function is common in patients with heart failure (HF), and is associated with increased morbidity and mortality. There is increasing evidence that transient increases in creatinine in the setting of acute HF are not prognostically important, whereas persistent deterioration does portend a higher mortality in this patient population. In addition, congestion seems to play an important role in the course of renal deterioration, and the combination of congestion and worsening renal function is the most significant clinical prognosticator in HF patients. This review aims to provide an update on the epidemiology and prognostic significance of RD in HF patients, in both the acute and the chronic setting.

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Renal dysfunction (RD) is a frequent comorbid condition and a major determinant of outcomes in patients with heart failure (HF). It is likely that the etiology of RD in patients with HF is much more complex than we first thought and represents a matrix of independent, albeit interacting, pathophysiological pathways with effects on both the kidney and the heart that share a common denominator: aging and inflammation. Renal dysfunction in HF has been attributed, among others, to biochemical, hormonal, and hemodynamic factors, coupled with pharmacological interventions. Regardless of the cause, the development of RD or worsening renal function is common in patients with HF, and is associated with increased morbidity and mortality. There is increasing evidence, however, that transient increases in creatinine in the setting of acute HF are not prognostically important, whereas persistent deterioration does portend a higher mortality in this patient population. In addition, congestion seems to play an important role in the course of renal deterioration, and the combination of congestion and worsening renal function is the most significant clinical prognosticator in HF patients. This review aims to provide an update on the epidemiology and prognostic significance of RD in HF patients, in both the acute and the chronic setting.

Introduction

Renal dysfunction (RD) is a frequent comorbid condition and a major determinant of outcome in patients with heart failure (HF) [1, 2]. Most patients with HF have mild or moderate RD [3], attributed to biochemical, hormonal, and hemodynamic factors, coupled with pharmacological interventions [4]. Regardless of the cause, the development of RD or worsening renal function (WRF) is common in patients with HF and associated with increased morbidity and mortality [5]. On the other hand, increasing evidence suggests that minor, transient increases in creatinine in the setting of acute HF are not prognostically important, whereas persistent deterioration does indicate irreversible damage that portends a worse outcome. In addition, congestion plays an important role in the course of renal deterioration, and

the combination of congestion and WRF is a significant clinical prognosticator in HF patients. In this review, we aim to provide an update on the epidemiology and prognostic significance of RD in HF patients, in both the acute and chronic setting.

The "cardiorenal syndrome" concept

The term "cardiorenal syndrome" has been attributed to a clinical condition that includes a variety of acute and chronic dysfunctions, in which the primary failing organ could be either the heart or the kidney; any primary impairment in one of the two organs promotes and perpetuates a complex combination of feedback mechanisms that further decrease the function of both the heart and the kidney [6]. Several pathways have been proposed as channels through which a crosstalk between the kidney and the heart takes place; the main ones are hemodynamic imbalance, neurohormonal signaling, and inflammatory activation [7]. On one side, pressure fluid overload and sodium retention, altered electrolyte levels and acidosis due to renal failure may contribute to ventricular dysfunction, accelerating cardiac remodeling and increasing the risk of arrhythmias. Conversely, myocardial dysfunction promotes the worsening of kidney function, such that a vicious circle is triggered; hypervolemia, renin-angiotensin-aldosterone system activation, inflammatory cytokines, nitric oxide dysregulation, oxidative and mechanical stress, and increase in myocardial oxygen consumption are all factors that lead to myocyte injury and death [8]. Therefore, in general, the incidence of cardiovascular events in RD patients increases as estimated glomerular filtration rate (eGFR) gets lower. The global rise in CKD has been met with apprehension and skepticism from the medical community [9]. It has been argued by some that we are facing a CKD 'epidemic' and by others that the high prevalence of CKD observed in different communities may be the result of flawed screening methods and tools. Both the estimation of GFR and the determination of microalbuminuria as markers of CKD have been criticized. Also, many have commented that CKD, as it is currently defined, is primarily a disease of elderly people with reduced kidney function. Some have described this as a physiological, age-related decline in kidney function, while others consider it to be pathological, warranting the label of a disease. The high prevalence of 'CKD' in the elderly population is likely to reflect the underlying high prevalence of overt and subclinical atherosclerosis and cardiovascular disease.

Biomarkers of renal function

For more than a century, clinicians have used serum levels of creatinine or creatinine-based derivatives as a marker of renal function. In fact, epidemiology studies evaluating RD have mostly focused either on serum creatinine itself or on calculated creatinine clearance using either the Cockroft-Gault or the 'modification of diet in renal disease' (MDRD) equations to estimate GFR. These various measures of renal function, however, have well-described drawbacks and are highly dependent on age, sex, body and muscular mass, and various other parameters [10]. Therefore, in some groups of patients, for instance those with muscle wasting or cardiac cachexia, creatinine-based measurements constantly underestimate the severity of RD.

Hypertension and CKD are tightly related, since high blood pressure is a major promoter of decline in GFR, irrespective of diabetic status, whereas the development of CKD is in itself a cause of secondary hypertension and can worsen preexisting hypertension, thus, increasing the incidence of both left ventricular hypertrophy (LVH) and resistant hypertension.

Blood urea nitrogen (BUN) concentration has emerged as a strong predictor of cardiovascular events, especially in the acute HF setting, and several studies suggest that it may be a more accurate marker of RD and a stronger prognosticator than creatinine in patients with HF [11, 12, 13]. BUN concentration better reflects intravascular hydration status and response to diuretic therapy as compared to creatinine [3, 14]. Since, half of filtered urea is reabsorbed in the renal tubules, BUN is as much a marker of renal tubular reabsorption as of GFR [14, 15]. In addition, BUN rises during periods of increased protein catabolism, such as in advanced or worsening HF, infection, and reduced dietary protein [16]. Even though this might be considered a weakness for a prognostic marker, there are in fact advantages with the use of BUN under these circumstances.

It has been suggested that some novel blood markers of RD, such as cystatin C, might be superior to creatinine in terms of predicting prognosis in patients with HF [1, 17, 18, 19]. Cystatin C is a more specific measure of GFR, and elevated plasma concentrations of cystatin C indicate a worse prognosis even when serum creatinine is normal [19, 20, 21]. The disproportionately high mortality in this situation most probably reflects deceptively low serum creatinine due to cardiac cachexia and a low skeletal muscle mass, where creatinine is known to underestimate GFR as previously discussed. Wen, *et al.* explored early markers of renal impairment in experimental post-myocardial infarction (MI) HF and found that it is the high blood cystatin C levels, rather than serum creatinine and BUN, that predict increased post-MI HF incidence [22]. However, the bulk of the literature is based on measures of renal function derived from creatinine-based measures of RD, and, therefore, the prevalence of RD classified by either cystatin C or urea is poorly described and will not be the subject of this review.

Renal dysfunction in chronic heart failure

Hypertension, left ventricular hypertrophy and chronic kidney disease

When compared to the general population, arterial hypertension is highly prevalent even in the early stages of CKD, reaching 86 % among people with end-stage renal disease (ESRD) [23]. Hypertension and CKD are tightly related, since high blood pressure is a major promoter of decline in GFR, irrespective of diabetic status, whereas the development of CKD is in itself a cause of secondary hypertension and can worsen preexisting hypertension, thus, increasing the incidence of both left ventricular hypertrophy (LVH) and resistant hypertension [24]. Very similarly, LVH is highly prevalent in patients with CKD and ESRD, attributed to both pressure and volume overload in this patient population, and has a significant negative prognostic impact, representing an independent risk factor for the development of arrhythmias, sudden death, and progression of HF [25]. Indeed, LVH has a prevalence of approximately 40 % in patients with CKD, and

increases with CKD progression, reaching a prevalence of 75 % in ESRD patients [26]. The multifactorial pathogenesis of LVH in renal patients, including both hemodynamic and non-hemodynamic stimuli that act synergistically, induce an increase in LV mass, and accelerate the process of uremic cardiomyopathy [27]. Arterial hypertension and anemia, which are associated with mineral metabolism abnormalities (hypocalcemia, hyperphosphatemia, low serum vitamin D levels, and secondary hyperparathyroidism), coupled with increased oxidative stress, arterial stiffness, hyperhomocysteinemia and endothelial dysfunction, all seem to be important factors that accelerate the process of atherogenesis, trigger pro-inflammatory and pro-thrombotic states in the glomerular and vascular endothelia, and aggravate the process of both CKD and LVH.

Prevalence of renal dysfunction in chronic heart failure

Most patients with HF have mild or moderate RD [3, 5]. In a meta-analysis including 16 studies and 80,098 hospitalized and non-hospitalized HF patients, 63 % had some degree of renal impairment (serum creatinine >1.0 mg/dL, eGFR <90 ml/min/1.73 m^2, or cystatin C >1.03 mg/dL), and 29 % had moderate to severe impairment (serum creatinine ≥1.5 mg/dL, eGFR <53 ml/min/1.73 m^2, or cystatin C ≥1.56 mg/dL) [28]. The candesartan in heart failure assessment of reduction in mortality and morbidity (CHARM) study provided data on the prevalence of RD in patients with chronic HF [29]. Based on estimates of GFR using the MDRD equation in 2,680 study participants, RD defined by an estimated GFR <60 ml/min/1.73 m^2 was reported in 36.0 % of patients (42.6 % for CHARM-Alternative, 33 % for CHARM-Added and 34.7 % for CHARM-Preserved) [29].

Prognostic importance of renal dysfunction in chronic heart failure

Regardless of the cause, the coexistence or the development of RD in patients with chronic HF has been associated, albeit not uniformly, with increased morbidity and mortality. In the aforementioned meta-analysis of 80,098 hospitalized and non-hospitalized HF patients [28], after a follow-up of ≥1 year, 38 % of patients with any renal impairment and 51 % with moderate to severe impairment died, versus 24 % who died without having impairment. Mortality increased across the range of renal function, with a 15 % higher mortality risk for every 0.5 mg/dL increase in creatinine and 7 % higher-risk for every 10 ml/min/1.73 m^2 decrease in eGFR [28]. The CHARM investigators provided important data on the impact of RD in a contemporary HF population [29]. In this large dataset, a creatinine-based estimate of RD proved to be prognostically useful and could help identify patients most at risk of future events. In the 2,680 study participants in whom baseline GFR was estimated using the MDRD equation, there was a stepwise increase in the incidence of cardiovascular death or admission for HF. Patients in the lowest GFR quintile (< 40 ml/min/1.73 m^2) had an almost three-fold higher rate of mortality, and the prognostic value of estimated GFR was similar among HF patients with preserved and reduced systolic function [29].

Regardless of the cause, the co-existence or the development of RD in patients with chronic HF has been associated, albeit not uniformly, with increased morbidity and mortality.

Renal dysfunction and heart transplantation

Jokinen, *et al.* studied the pre- and post-transplantation risk factors for acute renal failure requiring renal replacement therapy in 93 advanced HF patients who underWen,t orthotopic heart transplantation (HTx). Before HTx, 55 % of patients had normal renal function or mild renal failure (GFR >60 ml/min/1.73 m^2). Before discharge from the hospital, 25 % developed acute renal failure and required renal replacement therapy. Of these, 16 % had preoperatively normal renal function or mild renal failure, and 36 % had moderate or severe renal failure (GFR <60 ml/min/1.73 m^2) [30]. Similarly, Odim, *et al.* reported that renal failure before HTx is a significant risk factor for early postoperative renal replacement therapy [31]. Of note, the treatment of donors with low-dose dopamine (≈4 μg/kg/min) not only does not harm cardiac allografts, but also appears to improve the clinical course of the heart allograft recipient [32].

It should be noted, however, that RD is not always an independent predictor of adverse prognosis in advanced HF. Gradner, *et al.* prospectively studied 182 consecutive patients with advanced HF referred for consideration for HTx, with a median follow-up of 642 days. Forty patients died (13.2 % crude 1-year mortality), and the combined endpoint of all-cause mortality or urgent HTx was reached in 44 patients. Although eGFR was a univariate marker of all-cause mortality, the only independent predictor of either endpoint was an NT-proBNP concentration above the median [33]. Similarly, we have shown that among the various renal function parameters, BUN has a strong association with outcomes in patients with advanced HF, however the incremental value of renal function over Seattle HF score for risk determination was only marginal [34].

Renal dysfunction and left ventricular assist device implantation

Left ventricular assist device (LVAD) implantation is an established treatment option for patients with advanced HF, either as a bridge to transplantation or as destination therapy. Unloading of the heart after LVAD implantation improves circulatory parameters and, potentially, improves renal function. Data suggest that preoperative RD may adversely affect outcomes after LVAD placement. Butler and colleagues assessed 220 advanced HF patients who underWen,t LVAD placement [35]. Renal function improved substantially and rapidly across all baseline eGFR quartiles (< 47, 48–68, 69–95, and > 95 ml/min/1.73 m^2) post-LVAD implantation. Survival on LVAD was worse for patients with the worst baseline eGFR (42, 52, 63, and 79 % for 6-month and 26, 34, 47, and 66 % for 12-month survival for quartiles 1–4, respectively). Adjusting for other covariates, patients in the lowest eGFR quartile had a two-fold higher mortality rate post-implant. These data underscore the importance of careful patient selection for LVAD therapy. Of note, baseline renal function has been consistently identified as a multivariable predictor in preoperative clinical scores [36, 37, 38].

Renal dysfunction in acute decompensated heart failure

Prevalence of renal dysfunction in acute decompensated heart failure

The prevalence of RD in patients hospitalized with acute HF remained poorly characterized

until the publication of data from the Acute Decompensated Heart Failure National Registry (ADHERE) in 2007. ADHERE showed that the majority of these patients have significant renal impairment, which, in turn, influences treatment and outcomes [39]. In this large registry, 9.0 % of patients had normal renal function (GFR ≥90 mL/min/1.73 m^2) at admission, 27.4 % had mild RD (GFR 60–89 mL/min/1.73 m^2), 43.5 % had moderate RD (GFR 30–59 mL/min/1.73 m^2), 13.1 % had severe RD (GFR 15–29 mL/min/1.73 m^2), and 7.0 % had kidney failure (GFR <15 mL/min/1.73 m^2 or chronic dialysis). Despite this, only 33.4 % of men and 27.3 % of women were diagnosed with renal insufficiency. Diuretic dose, inotrope use, and nesiritide use increased, whereas angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker use decreased, with increasing RD. In the same registry, 22 % of patients had an abnormal admission BUN (>15 mmol/L, i.e., 43 mg/dL).

Several epidemiological studies, thereafter, consistently reported that approximately one out of three acute HF patients have some degree of RD. The main drawback in these studies was the lack of consistent RD definition. For example, if RD is defined as a serum creatinine >1.5 mg/dL (>130 μmol/L), then almost half of these patients have RD [39, 40, 41]. If serum urea is the preferred biomarker, then 50 % of acute HF patients will present with an admission value >28 mg/dL (>10 mmol/L). Finally, if RD is defined by CKD stages, then 90 % of patients with acute HF will have abnormal renal function at presentation, with about 25, 45, 15 and 5 % classified in stages II–V, respectively [40, 41, 42]. Another major drawback is the variety of inclusion and exclusion criteria in different studies and registries [43, 44]. For example, the inclusion of younger patients from Eastern Europe in the European registries [40, 41] systematically underestimates the magnitude of the problem as compared with the North American registries [39, 45]. Moreover, disparities in common risk factors for both heart and kidney failure (e.g., higher rates of obesity, hypertension and diabetes in North America) may further account for the observed differences.

Prognostic importance of renal dysfunction in acute heart failure

Admission Values

The ADHERE registry revealed that renal impairment at the time of admission influences treatment and outcomes [39]. In-hospital mortality increased from 1.9 % for patients with normal baseline renal function to 7.6 and 6.5 % for patients with severe dysfunction and kidney failure, respectively [39]. In fact, in the ADHERE risk tree, a risk model that can easily stratify acute HF patients into low-, intermediate-, and high-risk categories for in-hospital mortality [42], two out of the three parameters are biomarkers of renal function (serum creatinine and BUN), underscoring the importance of renal function in this patient population (Fig. 1).

More recently, using admission data from the PROTEC Trial (placebo-controlled randomized study of the selective a1-adenosine receptor antagonist rolofylline for patients hospitalized with acute decompensated heart failure and volume overload to assess treatment effect on congestion and renal function), O'Connor and colleagues developed a risk model for estimating 7-day HF events or death in patients admitted for acute HF [46]. The 7-day composite of death, HF rehospitalization or worsening HF was experienced by 14.6 % of patients, with a mortality rate of 1.8 %, HF rehospitalization rate of 0.5 %, and worsening HF rate of 13.1 %. In multivariable analyses, the strongest predictor of short-term morbidity and mortality was higher BUN concentration.

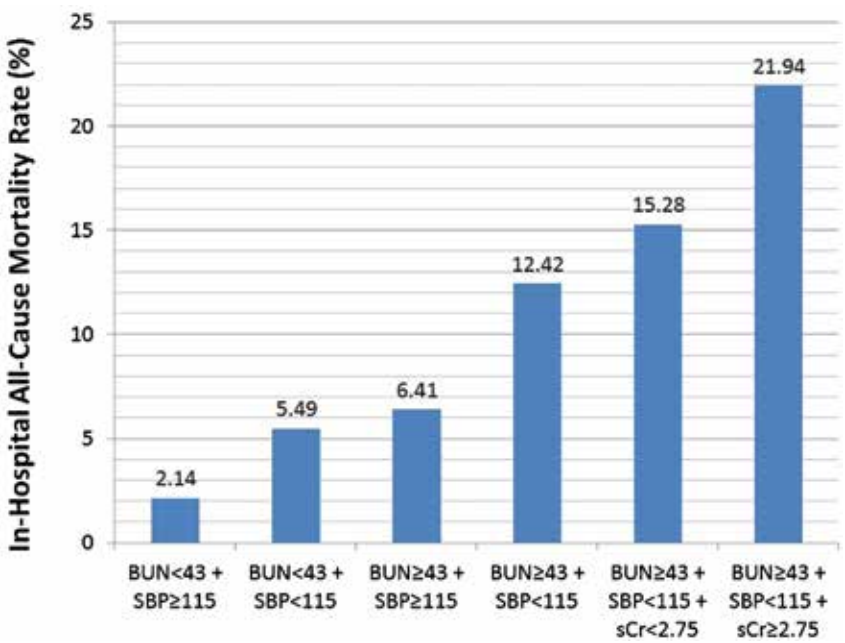

Fig. 1: Predictors of and risk stratification for in-hospital mortality in patients hospitalized with acute decompensated heart failure. Data from [42], Fig. 1.

Worsening of renal function during hospitalization

Worsening renal function during hospitalization for HF occurs often and has been associated with adverse outcomes. Various definitions of WRF have been used from time to time. Several studies have defined WRF function using various serum creatinine elevations, but the relative predictive value of such definitions is not constant. In a prospective cohort of 412 patients hospitalized for HF, Smith and colleagues evaluated the association of a wide spectrum of WRF definitions (absolute creatinine elevations ≥0.1 to ≥0.5 mg/dL and 25 % relative elevation from baseline) with 6-month mortality, readmission, and functional decline [47]. During the course of index hospitalization, serum creatinine elevation ≥0.1 mg/dL occurred in 75 % of patients, whereas elevation ≥0.5 mg/dL occurred in 24 % of patients. Higher creatinine elevations were associated with escalating mortality risk (Fig. 2). The maximum sensitivity of any definition for predicting mortality was 75 % and the maximum specificity was 79 %. High creatinine elevation was a more important predictor of death than was a single measure of baseline creatinine.

Most of the studies that sought to determine the incidence and risk factors of WRF in patients admitted with HF have defined WRF as an increase in serum creatinine levels of >0.3 mg/dL(26.5 μmol/L) at any time during hospitalization. In 1,681 older adults who were admitted with HF at 18 Connecticut hospitals, and who did not have clear precipitants for RD [48], WRF occurred in 28 % and was associated with six admission parameters: male gender, hypertension, rales >basilar, heart rate >100 beats/min, systolic blood pressure >200 mmHg, and admission creatinine >1.5 mg/dl. Based on these factors, risk for WRF ranged between 16 % (<1 factor)

and 53 % (>5 factors). After adjusting for confounding effects, WRF was associated with a 2.3-day longer stay, higher in-hospital cost by $1,758, and 2.7-fold higher in-hospital mortality.

Forman and colleagues, retrospectively, reviewed data from 1,004 consecutive patients admitted for a primary diagnosis of HF from 11 geographically diverse US hospitals [49]. WRF, defined as a rise in serum creatinine of >0.3 mg/dL, developed in 27 % of patients, and in the majority of cases, WRF occurred within 3 days of admission. History of HF or diabetes mellitus, admission creatinine ≥1.5 mg/dL (132.6 µmol/L), and systolic blood pressure >160 mmHg were independently associated with a higher-risk of WRF. Hospital deaths, complications, and length of hospitalizations >10 days were 7.5-, 2.1-, and 3.2-fold greater among patients with WRF.

In a study of over 20,000 US Medicare beneficiaries aged >65 years hospitalized with HF and discharged alive, 17.8 % developed WRF (serum creatinine increase by >0.3 mg/dL) during the index hospitalization [50]. One year after discharge, 35.4 % of these patients died, 64.5 % were readmitted, and average costs at 1 year were $14,829. After adjustment for patient characteristics and comorbid conditions, WRF was independently associated with 1-year mortality but not with readmission or total inpatient costs.

It has been suggested that even minor, transient increases in serum creatinine are associated with an adverse prognosis, and several studies, though not all, demonstrate a dose–response relationship. However, even if true, the relationship is not strong [3, 50]. Renal function based on serum creatinine measurements prior to admission might be a much stronger predictor of prognosis, because it is an objective measure of the underlying severity of chronic RD. Nevertheless, there is a general agreement that it is the persistent or the large increases in serum creatinine that portend a worse outcome. Of note, in contrast to changes in creatinine, transient increases in serum urea seem to be more frequently associated with adverse outcomes, and about half of patients will develop a substantial rise in serum urea during hospitalization, with 20 % developing an increase to levels >56 mg/dL (20 mmol/L). The aforementioned studies have consistently identified pre-existing RD, degree of congestion, HF severity, use of diuretics, diabetes mellitus, anemia, and either a very high blood pressure or a low one as determinants of WRF.

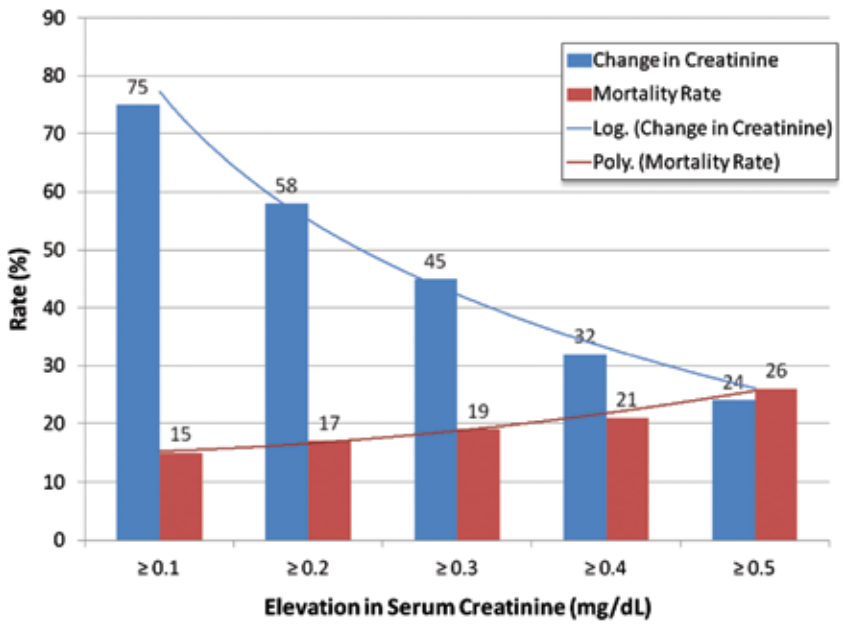

Fig. 2: Incidence of worsening renal function and 6-month mortality rates – and their trends – by various definitions based on serum creatinine elevations during hospitalization for heart failure. Data from [47], Table 1.

The role of congestion

Congestion due to volume overload is the main cause of hospitalization for patients with HF and is the most important therapeutic target in the acute setting. Correction of volume overload has a favorable effect not only on soft end-points, such as symptom relief and quality of life, but also on hard end-points, such as rehospitalization and all-cause mortality rate [51, 52]. However, this therapeutic goal is often not achieved, and patients with acute HF are frequently discharged with persistent symptoms and with minimal or no weight loss, or even weight gain, during the hospital stay [45]. Sodium and water retention lead to volume overload, increased filling and right-sided pressures, and result in elevation of venous pressure that is associated with renal impairment [53, 54]. Recently, Metra and colleagues demonstrated that WRF alone is not an independent determinant of outcomes in patients with acute HF; rather, it has an additive prognostic value when it occurs in patients with persistent signs of congestion at discharge [55]. Patients were subdivided into four groups according to the development or not of WRF and the persistence of ≥1 sign of congestion at discharge. Unexpectedly, patients with WRF and no congestion had similar outcomes compared with those with no WRF and no congestion. On the contrary, the risk of death or HF readmission was increased in the patients with persistent congestion alone and in those with both WRF and congestion (2.4-fold for mortality and 1.4-fold for mortality or rehospitalization).

Metra and colleagues demonstrated that worsening renal function alone is not an independent determinant of outcomes in patients with acute HF; rather, it has an additive prognostic value when it occurs in patients with persistent signs of congestion at discharge.

In a subsequent study, Aronson and colleagues investigated decongestion, central venous pressure, and risk of WRF in 475 patients with acute HF, of whom 238 underwent right-heart catheterization [56]. Right atrial pressure was measured at baseline and at 24 h, and net fluid loss was recorded in the first 24 h. WRF was defined as a >0.3 mg/dL increase in serum creatinine above baseline and occurred in 35.3 % of patients. There was a weak correlation between baseline right atrial pressure and baseline estimated GFR. The amount of fluid removed during the first 24 h did not correlate with the magnitude of right atrial pressure reduction, and no association was observed between WRF and baseline or the decrease in right atrial pressure. Therefore, right atrial pressure is not a reliable surrogate of decongestion and risk of WRF in the current acute HF population, contrary to previous reports from the evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness (ESCAPE) trial [57]. Importantly, in the study by Aronson, *et al.* [56], smaller early net fluid loss was strongly associated with increased risk for WRF; compared with the highest net

fluid loss tertile, the median and lower tertiles carried a 1.85-fold and 2.58-fold higher-risk for developing WRF, respectively. Therefore, aggressive decongestion might not be as detrimental as previously believed, and future research is necessary to determine if targeting congestion may help prevent WRF in this patient population.

The role of increased intra-abdominal pressure

Abdominal congestion, i.e., splanchnic, venous, and interstitial congestion, manifests in a substantial number of patients with advanced congestive HF, yet is poorly defined, and current pathophysiological models unsatisfactorily explain the detrimental link between congestion and RD. Compromised capacitance function of the splanchnic vasculature and deficient abdominal lymph flow resulting in interstitial edema might both be implied in the occurrence of elevated cardiac filling pressures and RD [58]. Indeed, raised intra-abdominal pressure, a marker of abdominal congestion, has been consistently correlated with RD in advanced congestive HF [58, 59, 60, 61, 62], providing evidence that alterations in the liver and spleen contribute to systemic congestion in HF. Preliminary data suggest that gut-derived hormones might influence sodium homeostasis, while the entrance of bowel toxins into the circulatory system – as a result of impaired intestinal barrier function secondary to congestion – might further depress cardiac as well as renal function [58]. Those toxins are mainly produced by microorganisms in the gut lumen, and undergo presumably important alterations in the case of advanced HF, especially when renal function is depressed.

Arrhythmic complications

The incidence of arrhythmic complications increases as eGFR decreases in HF patients. First, RD carries a higher incidence of atrial fibrillation; both the overall prevalence of AF and new onset AF are inversely related to eGFR, even after adjustment for the presence of hypertension and diabetes [63, 64]. Second, RD is associated with increased rates of sudden cardiac death. Patients with ischemic LV dysfunction in the MADIT-II study experienced a 17 % increase in sudden cardiac death for each 10 unit reduction in eGFR [65]. In the COMPANION study, among patients with ischemic LV dysfunction and LV dyssynchrony, RD was associated with a 69 % increased risk for sudden cardiac death [66]. Importantly, patients with reduced eGFR who received an implantable cardioverter defibrillator (ICD) had a significantly better survival compared to patients with reduced eGFR who did not receive an ICD [67]. Indeed, a study demonstrated that dialyzed patients have higher survival rates with an ICD (71 %) vs. their non-ICD counterparts (49 %) [68]. Renal dysfunction is independently related to a significant increase in the overall burden of appropriate ICD therapy in HF patients, regardless of the etiology. In fact, as renal function decreases, the time to the first appropriate ICD therapy is significantly shorter in terms of both time to first appropriate shock and time to first appropriate therapy. Hreybe, *et al.* [69] studied 230 consecutive patients who underWen,t ICD implantation and stratified them according to serum creatinine levels into three groups (<1 mg/dl, between 1 and 1.4 mg/dl, and>1.4 mg/dl). Subjects in the first group experienced a 3.8 % of ICD shocks in the first year of follow-up, whereas subjects in the third group had a 22.7 % rate of shock events during the same time. In this patient population, renal function was proven to be an independent predictor of the time to first appropriate ICD shock.

Protective measures

Regulation of the local angiotensin II receptor

Wen, *et al.* found that renal impairment in experimental post-myocardial infarction (MI) HF is associated with increased immunohistochemical staining of angiotensin II type 1 and type 2 receptor proteins, accompanied by increased renal fibrosis, tubular necrosis, and inflammatory cell infiltration. Treatment with losartan significantly attenuated upregulated angiotensin II type 1 but not type 2 receptors, decreased blood cystatin C levels, and attenuated renal fibrosis, tubular necrosis, and inflammatory cell infiltration [22].

Abdominal decongestion

Abdominal congestion has been consistently associated with RD and poor outcomes in advanced congestive HF [58, 59, 60, 61, 62]. Paracentesis, ultrafiltration, peritoneal dialysis, oral sodium binders, vasodilator therapy, renal sympathetic denervation, and agents targeting the gut microbiota present novel diagnostic as well as therapeutic strategies to achieve decongestion in HF accompanied by abdominal congestion [58].

Antagonizing the sympathetic nervous system

The sympathetic nervous system is detrimentally hyper-activated in systolic HF, especially in patients with RD [70]. Nebivolol is a third-generation beta-adrenergic receptor antagonist that has been shown to exert unique properties in this patient population [71]. To determine the safety and efficacy of nebivolol in elderly HF patients with RD, Cohen-Solal and colleagues used data for 2,112 patients from the SENIORS trial and divided them by tertile of eGFR [72]. eGFR was strongly associated with outcomes, and nebivolol was safe and had a similar protective effect in elderly HF patients with mild or moderate renal impairment.

Vasoactive agents

Low-dose dopamine [73], levosimendan [74], adenosine receptor antagonists [75], and tolvaptan [76, 77], all with different specific mechanisms, have been shown to be renoprotective to a lesser or a greater degree in some, but not in all, studies.

Conclusions

Renal dysfunction is a frequent comorbid condition and a major determinant of outcomes in patients with HF. There is increasing evidence that transient increases in creatinine in the setting of acute HF are not prognostically important, whereas persistent deterioration does indicate a higher mortality in this patient population. Congestion plays an important role in the course of renal function deterioration, and the combination of congestion and WRF is the most significant clinical prognosticator in HF patients, in both the acute and chronic setting. Future research is necessary to determine if targeting congestion may help prevent WRF and improve outcomes in patients with HF.

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ORIGINAL PAPER

Can we prevent or treat renal dysfunction in chronic heart failure?

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Prevention of renal dysfunction is possible in chronic heart failure (CHF) by treating comorbidities and underlying heart disease as well as by monitoring therapies with potential toxic renal effect. This paper summarizes the predictors of renal dysfunction and present strategies to prevent and/or treat renal dysfunction in CHF.

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We aimed to summarize the predictors of renal dysfunction and present strategies to prevent and/or treat renal dysfunction in chronic heart failure (CHF). Several factors may predict renal dysfunction in CHF, including older age, comorbidities (anemia, hypertension, diabetes), severity of underlying heart disease (systolic and diastolic dysfunction, central venous pressure) as well as certain therapies in specific circumstances (diuretics, nonsteroid acute inflammatory drugs, and renin-angiotensin-aldosterone (RAAS) inhibitors). Thus, prevention of renal dysfunction is possible in CHF by treating comorbidities and underlying heart disease as well as by monitoring therapies with potential toxic renal effect. At present, there is no specific treatment for renal dysfunction, but several new entities are under investigation. In conclusion, prevention of renal dysfunction is possible in CHF, but treatment is still under investigation. New studies are necessary to establish whether a specific algorithm may be used to prevent renal dysfunction in CHF patients.

Introduction

Methods used to quantify renal dysfunction in chronic heart failure (CHF) are similar to those used to quantify chronic kidney disease (CKD) in general. Serum creatinine is used because of its simplicity, although usually underestimates renal dysfunction, particularly in the elderly and in women [1]. Serum creatinine values >1.4 mg/dl are usually considered abnormal, and advanced kidney dysfunction is considered when serum creatinine levels >2.5 mg/dl. Given the limitations of serum creatinine measure, estimated measures of glomerular filtration rate (eGFR) calculated by formulas such as Cockcroft-Gault equation and especially modification of diet in renal disease (MDRD) equation are the preferred parameters of renal function [2, 3, 4]. In CHF, the prevalence of renal dysfunction defined by

eGFR <60 ml/min/1.73 m^2 ranges between 30 and 50 % [5, 6, 7], and it is a major predictor of prognosis [7, 8, 9].

Blood urea nitrogen (BUN) is extensively used as a marker of renal dysfunction and predictor of prognosis, particularly in patients with acute HF. Although a strong predictor of outcomes also in CHF [10, 11], it has been advocated that BUN is not as reliable an index of renal function as GFR [12]. This is because in addition to protein intake and catabolism, BUN is also dependent on tubular reabsorption of urea, which is mediated by arginine vasopressin, therefore, probably reflecting both neurohormonal activation (HF severity) and GFR [12].

Another method used to quantify renal dysfunction is the presence of increased levels of albumin in urine. Urinary albumin is also not entirely renal dependent, but current guidelines classify CKD in five stages based on eGFR and urinary albumin levels [13]. About 40 % of patients with CHF have increased levels of urinary albumin, which is an independent predictor of prognosis [14].

The high percentage of renal dysfunction in CHF may be because of the HF disease itself or simply because CKD is the initial cause of HF [13]. Most likely, the two pathways of renal dysfunction coexist and lead to adverse outcomes through independent mechanisms [8]. Overall, several mechanisms may explain the relationship between renal dysfunction and adverse outcomes, including renin-angiotensin-aldosterone (RAAS) activation, anemia, inflammation, oxidative stress, dyslipidemia, impaired coagulation as well as platelet dysfunction [15].

In this review, we aimed to summarize the predictors of renal dysfunction and to present several strategies to prevent and/or treat renal dysfunction in CHF.

Methods

We performed a literature review of randomized control trials (RCTs) and observational studies assessing predictors of renal dysfunction. CHF patients were defined as those discharged from the hospital after an acute episode or those registered in daily practice for CHF symptoms. We focused our analysis on CHF with reduced LVEF as (trial) data in patients with preserved LVEF are limited.

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Results

Prevention of renal dysfunction in chronic heart failure

We found no specific treatment for renal dysfunction, but several methods to prevent renal dysfunction in CHF. The prevention process of renal dysfunction can be seen as a chart-flow of several factors that apart and especially in combination may affect renal function, including (Fig. 1) *advanced age, comorbidities* (diabetes, hypertension/hypotension, anemia), *underlying heart disease* (LVEF, NYHA, congestion, venous pressure), and *potential "toxic" medication*—HF medication (diuretics, RAAS inhibitors) and non-HF medication (non-steroid acute inflammatory drugs—NSAIDs). Presence of renal dysfunction as a comorbidity plays a special role in this cycle, and its importance is discussed individually for each factor.

Advanced age in CHF

It is already known that elderly patients are at higher-risk of renal dysfunction due to multiple mechanisms, including loss of renal mass and tubules, arterial sclerosis, as well as interstitial fibrosis [16].

There are no RCTs studies assessing the efficacy and safety of RAAS inhibitors in elderly patients, the big majority with renal dysfunction. It is now accepted that an acute increase in serum creatinine of up to 25–30 % from baseline in response to ACE-I initiation is related to long-term renal protection, but this holds for patients with GFR >30 ml/min at baseline, corresponding in average to a serum creatinine levels up to 2.5–3.0 mg/dl [17]. Nevertheless, patients >65 years old or those with low body weight have a much lower GFR for a given serum creatinine, e.g., a GFR <30 ml/min occurs at serum creatinine levels as low as 2 mg/dl. This is very important, as actual CHF guidelines recommend adjustments in ACE-I therapy when serum creatinine >3–3.5 mg/dl [18], which may be too high for elderly patients. Thus, in the clinical setting, lower cut-off levels of serum creatinine or preferably GFR-based formulas should be used to adjust therapy and prevent occurrence of renal dysfunction in the elderly population.

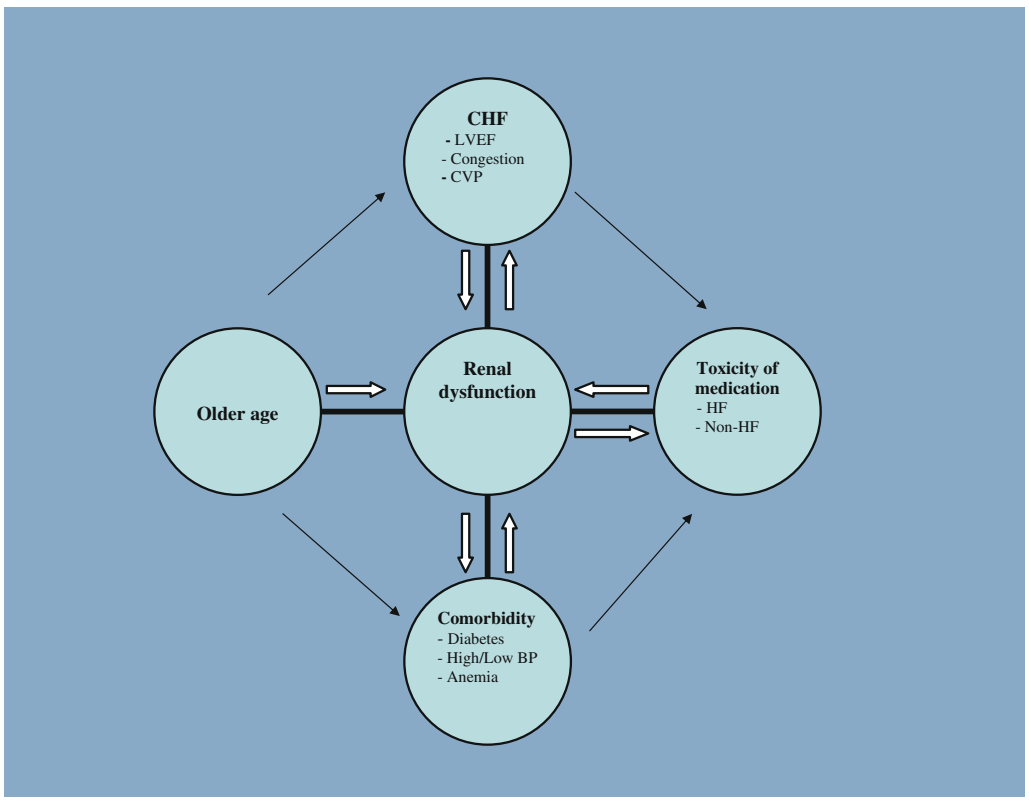

Fig. 1: Predictors of renal dysfunction in chronic heart failure. *CHF* Chronic heart failure, *LVEF* Left ventricular ejection fraction, *CVP* Central venous pressure, *BP* Blood pressure.

Comorbidities

Diabetes

In general, patients with diabetes are particularly at risk for renal complications. It is now accepted that a good control of glycemic levels will decrease the incidence of microvascular complications, including microalbuminuria [19]. In addition, it is well known that in patients with diabetes, treatment with RAAS agents prevents the occurrence of nephropathy and improves CV as well renal outcomes [20].

In a post hoc analysis of the SOLVD trial, treatment with enalapril prevented the occurrence of clinical proteinuria in diabetic patients, but not in non-diabetics [21]. However, this result may be explained by an insufficient power to detect a significant effect as the incidence of clinical proteinuria was very low in non-diabetic patients (1 %). However, treatment with enalapril resulted in a significantly greater reduction of hospitalizations in diabetic compared with non-diabetic CHF patients. Another post hoc analysis has also shown that treatment with enalapril had a protective effect on renal impairment compared with placebo in diabetic patients [22]. These data suggest that treatment with RAAS inhibitors may be particularly beneficial in diabetic CHF patients. Thus, a good control of glycemic levels and treatment with RAAS inhibitors are essential to prevent renal impairment in patients with diabetes and CHF, particularly when high urinary albumin concentrations are exhibited.

Blood pressure

Hypertension is known to be a risk factor for renal impairment, and appropriate blood pressure control will prevent renal complications [23]. A careful monitoring of high blood pressure levels is also important as roughly 50 % of patients with signs and symptoms of cardiac decompensation have systolic blood pressure >140 mmHg [24]. However, a big problem in CHF is the risk of hypotension, particularly in patients with advanced disease. In patients with severe CHF included in the CONSENSUS trial, the development of hypotension, and in particular low diastolic blood pressure, emerged as the strongest factor explaining an abnormal increase in serum creatinine during ACE-I therapy [25] In fact, a major challenge with CHF therapy nowadays is to dissociate the positive systemic effects of therapy from the negative effects on renal function, e.g., development of hypotension and renal hypoperfusion. Thus, both hypertension and hypotension should be avoided in the CHF setting to prevent renal dysfunction.

Both hypertension and hypotension should be avoided in the CHF setting to prevent renal dysfunction.

Anemia

Anemia is a common comorbidity in patients with CHF. A recent meta-analysis showed that as many as 37 % of CHF patients are anemic, and the presence of anemia doubles the risk of mortality [26]. The pathophysiology of anemia in CHF is very complex and still partly unclear. Importantly, however, is the bidirectional relationship between renal dysfunction and anemia. While reduced renal function will contribute to the occurrence of anemia, anemia itself will aggravate renal dysfunction via multiple mechanisms, including tissue hypoxia, blood pressure lowering, and neurohormonal activation [27]. Thus, treatment of anemia is important to prevent renal dysfunction and HF progression. However, it is still not clearly defined how to treat anemia in CHF. EPO treatment is successful in patients with severe kidney disease, but in patients with CKD has been shown to raise serious safety concerns [28]. In contrast, intravenous iron treatment may be an option for the treatment of anemia in CHF. In a study from Argentina, intravenous iron treatment was shown to improve renal function, cardiac function, as well as quality of life, without major safety issues [29]. A more recent study in patients with HF and iron deficiency, with or without anemia, has also shown that intravenous iron treatment improved symptoms, functional capacity, and quality of life, without safety concerns, but the study did not present the effect on renal function [30].

Underlying CHF disease

In the classical definition of the cardio-renal syndrome, renal function is affected in CHF patients because of the impaired hemodynamic status in relation to the underlying heart disease, e.g., decrease in LVEF (poor forward flow) [31]. In patients with mild to moderate CHF included in the SOLVD trial, low LVEF was associated with worsening of renal function (WRF) [22]. In contrast, in the VALIANT Echo Study, it was shown that left ventricular diastolic, rather than systolic dysfunction may better predict renal impairment [32]. In any case, both systolic and diastolic dysfunctions coexist in CHF, and development of diastolic dysfunction may be in fact one of the mediating mechanisms via which diabetes and older age affect renal function.

However, recently, central venous pressure (CVP) was also identified as an important predictor of renal function decline in patients with a broad range of CV disease including those with CHF [33]. Signs and symptoms of congestion, such as elevated jugular pressure, orthopnoea, or oedema, are also associated

Table 1: Predictors of worsening renal function in patients with CHF.

	Study population	No of patients	Predictors
Knight, *et al.* [22]	Patients with CHF treated with ACEI versus placebo (SOLVD trial)	3,379	Older age Diabetes Lower LVEF Diuretic dose Beta blocker (renoprotective)
Ljungman, *et al.* [25]	Severe CHF patients treated with ACEI (CONSENSUS trial)	243	Low DBP Diuretic dose (furosemide)
Juhlin, *et al.* [41]	Patients with CHF treated with ACEI (RCT)	10	NSAID diclofenac (acute administration)
Damman, *et al.* [33]	Broad spectrum of CVD, including CHF (observational study)	2,557	Central venous pressure

CHF Chronic heart failure, *LVEF* Left ventricular ejection fraction, *CVD* Cardiovascular disease, *DBP* Diastolic blood pressure, *NSAID* Non-steroid acute inflammatory drugs.

with renal impairment [34]. These findings challenged the traditional idea that only cardiac index, poor forward flow and hypoperfusion is the main cause of renal insufficiency [35] and shown that also hypervolemia (so called backward flow) is associated with renal impairment, probably by transmitting venous congestion to renal veins. Nevertheless, the relation between CVP and GFR is about half as strong as the relation between renal blood flow and GFR, suggesting that the hemodynamic component is still primordial for renal impairment within cardiorenal syndrome [36].

All in all, these factors underline the importance of treating the underlying heart disease in order to prevent renal impairment. From existing life-saving therapies, beta blockers have been shown to be a safe choice to prevent renal impairment, in both patients with or without an ACEI [22].

Studies assessing predictors of renal dysfunction in CHF are summarized in Table 1.

Potential toxicity of medication

NSAIDs

Aspirin inhibits the prostaglandin-mediated dilation of the glomerular afferent arteriole and may, thus, further decrease GFR, especially when combined with RAAS antagonists, which cause efferent glomerular arteriole dilation [37]. The WATCH trial assessed the use of warfarin versus antiplatelet (aspirin and clopidogrel) therapy in CHF patients. The trial showed that the use of aspirin (but not clopidogrel), was associated with more hospitalizations for worsening HF than the use of warfarin [38]. In fact, a post hoc analysis of the SOLVD trial has shown that patients who use antiplatelet agents will benefit less from enalapril therapy [39]. Also, observational studies have shown that the use of aspirin may attenuate the benefit of ACE-inhibitors in patients with high serum creatinine levels [40]. Instead, in a small RCT, acute prescription of diclofenac and not long-term low-dose aspirin was associated with renal function decline [41]. All in all, these data suggest that NSAIDs should be avoided in patients with CHF, particularly in those with already existing renal dysfunction, in order to draw a maximum benefit from ACE-I therapy. Replacement of aspirin with clopidogrel could be indicated to prevent renal dysfunction while maintaining antithrombotic therapy.

Loop diuretics

One of the most debated therapies in CHF is the use of loop diuretics. Several studies have already pointed out that loop diuretics, particularly in high doses will increase the risk of death [22, 25, 42]. Several mechanisms may explain these deleterious effects, including decrease in blood pressure and renal hypoperfusion, stimulation of the RAAS activation, and potassium-related complications [43]. It seems that the relation between loop diuretics and mortality has a U-shape form, with small doses improving the prognosis while high doses having a deleterious effect. Other therapies of fluid removal, such as ultrafiltration, at a rate that does not exceed the interstitial fluid mobilization rate, may avoid RAAS activation (29). Preliminary results from

It is now accepted that an acute increase in serum creatinine of up to 25 % from baseline in response to RAAS agents is related to long-term renal protection. It was pointed out that the beneficial effects hold also for patients with moderate renal dysfunction, that is, for those with a baseline GFR 30-60 ml/min.

UNLOAD (ultrafiltration of IV Diuretics for Patients Hospitalized for Acute decompensated heart failure) showed a lower rehospitalization rate in patients assigned to ultrafiltration, compared with those on standard treatment [44]. Thus, given the actual data, prescription of high doses of loop diuretics, particularly on long-term, are not recommended in CHF.

RAAS agents

Prescription of RAAS agents in patients with renal disease is a debated topic given the risk of these agents to induce worsening of renal function and hyperkalemia [45, 46]. It is now accepted that an acute increase in serum creatinine of up to 25 % from baseline in response to RAAS agents is related to long-term renal protection. It was pointed out that the beneficial effects hold also for patients with moderate renal dysfunction, that is, for those with a baseline GFR 30-60 ml/min [17, 18]. Thus, the benefits of RAAS therapy should be hold between these limits and may not be extrapolated to patients with eGFR <30 ml/min or those with a steep increase in serum creatinine (>25 % increase from baseline within 2 months of treatment).

Serum potassium levels increase in parallel to renal function decline, and hyperkalemia becomes especially an issue in patients with GFR <40 mg/dl [47]. In susceptible patients, in addition to RAAS inhibitors, other factors, such as potassium-sparing diuretics, potassium supplements, as well as diet may also increase the risk of hyperkalemia, while thiazide diuretics decrease the risk. Further on, the risk is increased in patients with diabetes [48]. Thus, a close monitoring of serum electrolytes is required particularly in these patients, both at initiation of therapy and during follow-up. Nevertheless, given the benefits of RAAS agents, corrective measures rather than denying the therapy should be preferred. These measures include discontinuation or caution in prescribing therapies with hyperkalemic potential, such as potassium-sparing diuretics, potassium supplements, as well as NSAIDs [49]. An individual approach is, thus, necessary to retrieve the maximum benefit from RAAS therapy in CHF patients with renal dysfunction.

New perspective for treatment of renal dysfunction in chronic heart failure

Biodesigner peptides

At present, a challenge with existing therapies is to associate their systemic, e.g., decrease in blood pressure hemodynamic effects with unfavorable renal effects. Thus, several therapeutic compounds that act through different mechanisms, have being tested. These compounds are generated through engineering of proteins and are based on fusing beneficial elements of two peptides in order to create a new one, with better therapeutic properties. Such an example is C-type natriuretic peptide (CNP), which resulted from incorporation of structural determinants of B-type natriuretic peptide (BNP) and atrial natriuretic peptide (ANP). C-type natriuretic peptide (CNP) has shown less hypotensive effects and more GFR-enhancing properties when compared with BNP [50]. Another example of biodesigner peptide is alternatively spliced BNP (ASBNP). This peptide has also shown to retain renal effects while lacking vascular effects of BNP in a canine model of CHF [51]. Specifically, ASBNP did not alter

mean arterial pressure and increased GFR; also, ASBNP suppressed plasma renin and angiotensin II while inducing natriuresis and diuresis compared with BNP. These new peptides show promise as therapeutic agents for cardiorenal syndrome, but future studies are required to conclude on their effects in humans.

Summary and future direction

Current findings

In this study, we showed that several factors may affect renal function in CHF, including aging, comorbidities (anemia, hypertension, diabetes), underlying heart disease (LVEF, CVP) as well as some therapies (NSAIDs, diuretics, RAAS). Therefore, treatment of comorbidities and treatment of underlying heart disease as well as adjustment of therapy are potential tools for prevention of renal dysfunction. Paradoxically, patients with prevalent renal dysfunction may benefit less from existing therapies given the safety issues. Treatment with RAAS inhibitors

Treatment with RAAS inhibitors is essential for CHF treatment, but close monitoring and an individual, rather than a generalized approach, is necessary to retrieve a maximum benefit, particularly in patients with prevalent renal dysfunction.

is essential for CHF treatment, but close monitoring and an individual, rather than a generalized approach, is necessary to retrieve a maximum benefit, particularly in patients with prevalent renal dysfunction. Finally, we showed that several new natriuretic peptides derivatives show promise for the treatment of renal dysfunction.

How renal function should be measured in future CV trials

At present, the creatinine-based MDRD formula is the method of election for renal function assessment in CHF [4, 13]. However, this method was rarely used in CHF trials, and most studies relied on Cockcroft-Gault formula or even worse, on simple serum creatinine measurement to assess baseline or worsening renal function. Furthermore, most CHF trials did not assess urinary albumin excretion, although it is a marker of initial stages of renal dysfunction. Presence of albuminuria may also be in particular an indication for RAAS prescription [52]. Recently, it has been emphasized the importance of integrating both albuminuria and eGFR for the assessment of renal dysfunction, as the two methods complement and not compete with each other [53]. Despite limitations, the use of BUN or a combination of BUN and creatinine should be probably also more explored as a measure of renal function in CHF, as its use was primarily investigated in acute HF.

The use of serum creatinine and even creatinine-based methods to assess renal dysfunction may clearly underestimate early renal function decline as serum creatinine elevates only when GFR is considerably decreased [1]. Thus, the measurement of new biomarkers such as cystatin C [54], kidney injury molecule 1 (KIM-1), and neutrophil gelatinase-associated lipocalin (NGAL) may be more sensitive methods for early detection and prevention of renal impairment [55]. However, more studies are necessary to assess the role of these new biomarkers in the CHF setting.

Worsening of renal function: always a bad sign?

In line with the existing evidence, one would implicitly consider worsening of renal function at least a safety, if not an efficacy parameter, when assessing a drug benefit-risk profile. However, it does not necessarily imply that worsening of renal function *per se* is associated with worse hard outcomes. The best example is probably the RAAS therapy. Conversely, it does not necessarily imply that an improvement in renal function by therapy is followed by an improvement in hard outcomes, and in this regard, the ONTARGET trial may be a good example [56]. In ONTARGET, the combination of an ACEI and ARB decreased urinary albumin excretion and blood pressure more than the single treatment groups; however, the combination did not offer more protection on the combined outcome of doubling of serum creatinine, dialysis of death. Of the components of the composite end-point, the incidence of death exceeded the incidence of renal end-points, and the majority of deaths were due to cardio- or cerebrovascular disease [20]. This outlines the importance of drug safety, as the positive effects of a drug may be counterbalanced by its side effects.

In conclusion, prevention of renal dysfunction is possible in CHF by treating comorbidities and underlying heart disease as well as by monitoring therapies with potential toxic renal effect. At present, there is no intervention specifically targeted at renal function, but several new entities are under investigation. In addition to new therapies, new methods of assessing renal dysfunction are required.

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Does limiting salt intake prevent heart failure? A critical appraisal

Mathew C. Konerman, Scott L. Hummel

High dietary sodium intake is associated with several factors that promote the development of heart failure (HF) including systemic hypertension, ventricular hypertrophy, diastolic dysfunction, vascular stiffness, and endothelial dysfunction. Some argue that sodium restriction actually may contribute to the development of HF through increased neurohormonal activation. The effect of sodium intake on HF risk may depend on an individual's "salt-sensitivity." Currently available cohort studies have not fully clarified the links between sodium intake and incident HF. This review evaluates the evidence supporting sodium restriction as a means to prevent HF.

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Reducing the incidence of heart failure (HF) and its associated morbidity, is a major goal for public health authorities. In this review, we evaluate the evidence supporting sodium restriction as a means to prevent HF. High dietary sodium intake is associated with several factors that promote the development of HF including systemic hypertension, ventricular hypertrophy, diastolic dysfunction, vascular stiffness, and endothelial dysfunction. Some argue that sodium restriction actually may contribute to the development of HF through increased neurohormonal activation. The effect of sodium intake on HF risk may depend on an individual's "salt-sensitivity." Due in part to methodological limitations, currently available cohort studies have not fully clarified the links between sodium intake and incident HF. Future research is needed to determine accurate and reproducible methods of measuring sodium intake and to identify factors which may make specific individuals more vulnerable to developing HF in the setting of high sodium intake.

Introduction

According to nationally representative survey data, nearly six million Americans currently are living with heart failure (HF), with annual costs of care over $32 billion [1]. As the US population ages, the prevalence of HF is expected to increase by nearly 25 % over the next 15 years [2]. As a result, reducing the incidence of HF and its associated morbidity has become a major goal for public health authorities. While pharmacological strategies certainly play a major part in this effort, "lifestyle-based" factors such as dietary modification could potentially decrease the individual and societal burden of HF [3, 4].

Dietary sodium restriction is the most commonly recommended self-care behavior in patients with HF and has been called a "cornerstone of HF disease management" [5, 6]. Yet current guidelines vary widely in their recommendations regarding the importance of and appropriate threshold for daily sodium intake in patients with existing HF [7, 8, 9], in part due to conflicting results from observational cohorts and interventional studies. Interpreting the relationship between dietary sodium intake and incident HF may be even more challenging.

The rationale for advocating sodium restriction to prevent HF stems largely from studies associating high sodium intake with hypertension, a major HF risk factor [10, 11, 12]. Cohort and interventional studies also link high sodium intake with cardiovascular structural and functional changes that predispose to the development of HF. However, some point out that sodium restriction increases neurohormonal activation that could promote cardiovascular disease, including HF [13]. Few studies have directly evaluated the impact of sodium restriction on HF incidence. In this review, we will explore the data supporting sodium restriction in the prevention of HF, acknowledge counterarguments, outline methodological challenges, and propose research topics to clarify the relationship between sodium intake and incident HF.

Sodium Intake and hypertension – an important HF risk factor

In a landmark cohort study that followed 5,143 patients from the Framingham Heart Study and Framingham Offspring Study for a mean of over 20 years, Levy, *et al.* identified hypertension as the most common risk factor for HF, predating the development of HF in 91 % of cases and accounting for over 40 % of the population-attributable risk for HF [14]. Further analysis of the Framingham cohort revealed that the lifetime risk of HF doubles with a blood pressure ≥160/100 vs. 140/90 mmHg [12]. Uncontrolled systolic hypertension is a particularly important risk factor for the development of HF in older adults [10, 11], and pharmacological treatment of uncontrolled systolic hypertension (SBP >160 mmHg) even in very elderly subjects strongly reduces the incidence of HF [15].

High sodium intake has long been considered one of the main modifiable factors promoting hypertension in populations [16]. Recently, the global Prospective Urban-Rural Epidemiology Study demonstrated a dose-response relationship between estimated 24 h urinary sodium excretion (as an index of intake) and blood pressure of 2.11 mmHg increase in systolic blood pressure per gram of sodium excretion. This relationship was present across all geographic regions, and the slope of the relationship between blood pressure and estimated sodium intake was steeper in older subjects and those with hypertension [17]. A recent Cochrane group meta-analysis of 34 randomized trials including 3,230 hypertensive and non-hypertensive participants also confirmed a dose-response relationship between salt (sodium chloride) intake and blood pressure across a range of 3 to 12 g/day [18].

A prominent example of the dose-response relationship with blood pressure comes from the DASH-Sodium study, which compared the blood pressure lowering effects of the dietary approaches to stop hypertension (DASH) eating pattern vs. a control diet in 412 subjects with prehypertension or early hypertension. Within each diet group assignment, individuals were assigned in random sequence to 30 days each of high (150 mmol/day), intermediate (100 mmol/day), and low (50 mmol/day) sodium intake. In both the DASH and control diet groups, reduction in sodium intake lowered systolic and diastolic blood pressures in a stepwise fashion. When compared to a control diet with high sodium intake, a DASH diet with low sodium intake was associated with a mean systolic blood pressure that was 7.1 mmHg lower in participants without hypertension and 11.5 mmHg lower in participants with hypertension [19].

Sodium intake and cardiac damage/dysfunction

The strongest link between sodium intake and structural HF risk factors is the association with left ventricular hypertrophy. This relationship was first observed in a small cohort of middle-aged hypertensives, where 24 h urinary sodium was the strongest predictor of left ventricular mass [20]. This relationship has since been confirmed in multiple studies enrolling hypertensive and normotensive subjects [21, 22, 23, 24]. The Treatment of Mild Hypertension Study, performed in 844 mildly hypertensive men and women, found that urinary sodium excretion correlated as strongly with left ventricular mass as systolic blood pressure and body mass index [24]. Jin, *et al.* studied 317 untreated patients (21 % with hypertension), finding that higher sodium excretion predicted increased left ventricular mass by echocardiography [22]. A similar relationship has been observed even in healthy young adults. Rodriguez, *et al.* evaluated data from 1,042 participants (age 30 ± 4 years) enrolled in the Coronary Artery Risk Development in Young Adults (CARDIA) Study. Only 4 % of the study's participants were hypertensive. Using multiple 24 h measurements of urine sodium to assess sodium intake, they observed that participants in the highest versus lowest quartile of urinary sodium excretion had significantly greater echocardiographic left ventricular mass index (37.5 versus 34.0 g/m^2.7; $p < 0.001$) [23]. On balance, these studies suggest that the relationship between sodium intake and left ventricular mass is not wholly mediated by blood pressure effects.

In addition, sodium restriction has been associated with regression of left ventricular hypertrophy [25]. In a trial of 76 untreated patients with mild-moderate hypertension, Jula, *et al.* randomized half to receive instruction aimed at reducing sodium intake to 70 mmol/day. Dietary records and 24 h urine sodium measurements were obtained at baseline and every 3 months for 1 year. Sodium excretion was substantially reduced in the intervention group (195 to 94 mmol/24 h at 6 months and 109 mmol/24 h at 12 months). This was associated with significant decreases in systolic (8.9 mmHg, $p < 0.001$) and diastolic blood pressure (6.5 mmHg, $p < 0.001$) at 6 months that persisted through 12 months. In addition, sodium-restricted individuals had approximately 5 % reduction in left ventricular mass (238 ± 63 to 225 ± 51 g, $p < 0.01$); this effect was more pronounced in subjects with left ventricular hypertrophy at baseline.

The strongest link between sodium intake and structural HF risk factors is the association with left ventricular hypertrophy. Sodium restriction has been associated with regression of left ventricular hypertrophy.

In contrast to structural remodeling, the impact of sodium intake on cardiac function has been less extensively studied. Langenfeld, *et al.* obtained 24 h urine sodium measurements in 44 young male patients with mild, untreated hypertension and 45 male normotensive controls. In hypertensives, high urinary sodium excretion was the strongest predictor of impaired diastolic filling by echocardiography [26]. In a placebo-controlled crossover study, sodium loading with salt tablets over a 5-day period in 16 normotensive individuals reduced color M-mode flow propagation velocity, suggesting increased ventricular stiffness [27]. However, large cohort studies do not support a strong relationship between dietary sodium intake and diastolic function. In 1,064 Native Americans ≤40 years of age from the Strong Heart Family Study, questionnaire-estimated sodium consumption was modestly related to atrial filling fraction, but not other diastolic function indices [28]. Lee, *et al.* studied 2,362 normotensive Korean subjects, finding

no relationship between spot urine-estimated sodium excretion and echocardiographic diastolic function [29]. These inconsistent findings highlight the need to further explore the relationship between sodium intake and diastolic dysfunction, an important precursor to HF [30].

Sodium Intake and Vascular Damage/ Dysfunction

Increased arterial stiffness can affect both ventricular systolic and diastolic function, key components in HF pathophysiology. In normotensive Australian subjects, very low habitual sodium intake (15–68 mmol/day sodium excretion) predicted lower aortic pulse-wave velocity independent of blood pressure and appeared to blunt age-associated arterial stiffening [31]. This relationship has been directly observed in older hypertensives, a group particularly at risk for developing incident HF. Gates, *et al.* randomized 12 older patients with stage 1 hypertension in crossover fashion to low and normal sodium intake (54 vs. 135 mmol/day sodium excretion) for 4 weeks each. After 1 week of sodium-restriction, ultrasound-measured carotid artery compliance had increased by 27 % and was 46 % higher by the end of the low sodium period [32]. In another crossover-randomized study, 35 hypertensives consumed 60, 150, and 200 mmol/day of sodium for 4 weeks each. Despite suppression of renin activity and aldosterone, carotid-femoral pulse wave velocity was approximately 5 % higher during the 150 and 200 mmol/day time periods. The effects of sodium intake on arterial stiffness appeared at least partially blood pressure-independent [33].

Conduit artery endothelial dysfunction is prognostically important in established heart failure with reduced ejection fraction and, in some cases, may play an important role in its initiation and progression [34]. Paulus and Tschope recently proposed a new paradigm for heart failure with preserved ejection fraction that emphasizes the importance of microvascular endothelial dysfunction [35]. Tzemos and colleagues crossover-randomized 16 normotensive men to placebo or 200 mmol/day salt tablets and studied vascular reactivity with forearm venous occlusion plethysmography. They observed that during the high sodium intake period, endothelium-dependent vasodilation was significantly blunted in comparison to the control period [36]. Jablonski, *et al.* recently extended these findings in 17 older hypertensive patients (11 men, 6 women, aged 62 ± 7 years). In a randomized crossover study, participants consumed low- and high-sodium diets (153 vs. 70 mmol/day 24 h urinary excretion) for 4 weeks each. In comparison with the high-sodium period, flow-mediated dilation of the brachial artery was 68 % greater during low sodium intake; this finding was related to increased nitric oxide bioavailability [37].

Increased sodium intake is also associated with increased urinary albumin excretion, a marker of microvascular dysfunction and cardiovascular risk. The relationships between diabetes mellitus, chronic kidney disease, and albuminuria are well-known. However, even in hypertensive patients without chronic kidney disease or diabetes, high sodium intake is closely related to the degree of urinary albumin excretion [38]. This association between sodium intake and urinary albumin excretion is more pronounced in obese individuals, and sodium restriction reduces urinary albumin excretion in hypertensive patients [39, 40]. This may be particularly relevant for HF prevention given that albuminuria has been associated with echocardiographic markers of impaired cardiac function. In a study of 1,894 hypertensive patients, Katz, *et al.* found that even low levels of albuminuria was associated with decreased global longitudinal strain and increased *E/e'* ratio, indicating impaired left ventricular systolic and diastolic function [41].

> The answer to the question of whether sodium restriction prevents HF may depend on differences in individual response to sodium intake. In both normotensive and hypertensive humans, a salt-sensitive blood pressure pattern consistently increases long-term overall mortality and cardiovascular morbidity independent of baseline blood pressure.

Sodium intake and volume overload

High sodium intake and related volume overload could promote HF in groups at particularly high-risk for sodium retention. Impaired natriuresis occurs early in the course of HF [42], and as HF progresses, increased plasma volume is common [43]. In addition to direct effects on intraventricular filling pressures, volume overload has other detrimental consequences that could promote HF. These include increased cardiac venous pressure that impairs subendocardial perfusion and increased myocardial oxygen requirement due to elevated wall stress [44]. Mckie, *et al.* recently compared the natriuretic response to volume expansion with intravenous normal saline over 60 min in young healthy controls and subjects with pre-clinical systolic or diastolic ventricular dysfunction (individuals that, by definition, did not endorse HF symptoms). In contrast to controls, individuals with pre-clinical ventricular dysfunction did not increase sodium excretion in response to saline infusion [45]. Moreover, emerging data suggest that volume overload states directly cause oxidative stress, inflammation, and local neurohormonal activation in the vasculature [46, 47].

Sodium restriction and neurohormonal activation

The current understanding of HF pathophysiology implicates chronic activation of the renin-angiotensin-aldosterone, sympathetic, and other neurohormonal systems. The argument against sodium restriction in the prevention of HF is based on its relationship with neurohormonal activation. In a Cochrane meta-analysis of 167 studies randomizing normotensive and/or hypertensive subjects

to low-sodium and high-sodium diets, a sodium-restricted diet was associated with increased plasma levels of renin, aldosterone, epinephrine, and norepinephrine [48]. Increased neurohormonal activation, very well, may account for the relatively modest reduction in blood pressure with sodium restriction in this meta-analysis (BP decrease of 1 % in normotensives and 3.5 % in hypertensive patients) [48]. It is worth noting that a similar neurohormonal response to sodium restriction has been observed in HF patients and has led to debate regarding whether sodium should be restricted even in prevalent HF [49, 50].

"Salt-Sensitivity" and HF Risk

The answer to the question of whether sodium restriction prevents HF may depend on differences in individual response to sodium intake. Controlled feeding studies have identified subjects with a "salt-sensitive" blood pressure phenotype; that is, blood pressure rises with high sodium intake versus low sodium intake. This differs from the "salt-resistant" phenotype, reflecting a minimal blood pressure response to changes in sodium intake [51]. In both normotensive and hypertensive humans, a salt-sensitive blood pressure pattern consistently increases long-term overall mortality and cardiovascular morbidity independent of baseline blood pressure [52, 53].

The following factors highly prevalent in HF cohorts are associated with blood pressure salt-sensitivity: advanced age, systemic hypertension, central obesity, sleep apnea, insulin resistance, and chronic renal insufficiency [54, 55, 56, 57]. In addition, diurnal blood pressure non-dipping, the failure of blood pressure to decline during sleep, is closely linked to salt-sensitivity and predicts incident HF [51, 58]. Compared to salt-resistant persons, salt-sensitive subjects have impaired natriuresis and are more prone to develop HF-associated cardiovascular abnormalities including left ventricular hypertrophy, larger left atrial size, ventricular diastolic dysfunction, and microvascular disease independent of baseline blood pressure [59, 60]. Salt-sensitive animals develop HF during high sodium intake, with mechanisms including increases in oxidative stress, vascular inflammation, and "local" activation of neurohormonal systems in the kidney, heart, and vasculature [61, 62]. Preliminary data suggest that human hypertensive HF may have a similar phenotype [63, 64].

The salt-sensitive phenotype has, classically, been ascribed to impaired nighttime renal sodium excretion and the need to increase glomerular perfusion pressure to balance excretion with intake [51]. However, intriguing recent data indicate that a substantial amount of ingested sodium is stored non-osmotically in the skin and other organs and that the amount of stored sodium increases with age and in the setting of hypertension [65]. The endothelial glycocalyx, a thin glycosaminoglycan layer that lines blood vessels, may also play a key role in buffering ingested sodium and mediating the likelihood and extent of salt-induced vascular damage and dysfunction [66]. The relationship of these factors to classically determined salt-sensitivity and cardiovascular outcomes, including any association with incident HF, remains to be determined.

Sodium intake and HF risk in cohort studies

Few studies have directly investigated the relationship between sodium intake and incident HF. He, *et al.* estimated sodium intake using a single 24 h dietary recall in over 10,000 participants from the 1st National Health and Nutrition Examination Survey prospective cohort study [67]. They observed that the cumulative incidence of HF in overweight and obese patients increased significantly with a sodium intake of greater than 114 mmol/day. Other aspects of diet are likely important, since outside of clinical research investigations sodium restriction occurs as part of a whole food diet rather than in isolation. Levitan, *et al.* utilized food frequency questionnaires to assess adherence to a DASH diet pattern in Swedish men and women without a history of HF, myocardial infarction, or diabetes. In a study including 36,019 women, the highest quartile of DASH diet adherence was associated with a significant 37 % reduction in HF incidence compared to the lowest quartile [68]. Similarly, in a study including 38,987 men, the highest quartile of DASH diet adherence was associated with a significant 22 % reduction in HF incidence compared to the lowest quartile [69]. While these studies did not focus solely on sodium intake, this factor constituted 1/8 of the scoring system to determine DASH dietary pattern adherence. In contrast to these findings, Del Gobbo, *et al.* recently reported on the relationship between incident HF and adherence to four recommended dietary patterns (determined using food frequency questionnaires and including the DASH diet) in 4,490 older adults with over 21 years of follow-up in the Cardiovascular Health Study. The primary analysis, adjusted for other common clinical risk factors as well as physical activity, demonstrated no association between dietary patterns and incident HF. However, supplementary data revealed that subjects in the highest vs. lowest quintile of sodium intake had a 15 % higher-risk for developing HF. In participants without baseline coronary heart disease, the highest quintile of sodium intake presented 25 % greater risk for incident HF, with highly significant ($p = 0.009$) trend across categories of sodium intake following extensive adjustment for other risk factors [3].

> Recent cohort studies challenge the notion that dietary sodium restriction prevents HF. Controversy also exists regarding the relationship between sodium intake and cardiovascular events, such as myocardial infarction, which predispose individuals to developing HF.

Other recent cohort studies challenge the notion that dietary sodium restriction prevents HF. In a large, observational study including 101,945 subjects from 17 countries, O'Donnell, *et al.* evaluated the relationship between urinary sodium and potassium excretion on mortality and cardiovascular events [70]. A morning spot urine sodium measurement was utilized to estimate 24 h urinary sodium. While the study's primary outcome was a composite cardiovascular endpoint, a subgroup analysis revealed no relationship

between sodium excretion and incident HF. Of note, an estimated sodium intake between 3–6 g/day was associated with a lower risk of death and cardiovascular events compared to higher or lower levels of intake. A previous study by the same group, again with estimated daily sodium intake from morning spot urine samples, suggested a similar "J-shaped" relationship between sodium intake and cardiovascular mortality among 28,880 clinical trial patients at high-risk of cardiovascular events. In this study, estimated sodium intake above 7 g/day and below 3 g/day was associated with increased risk of hospitalization for HF [71]. Kalogeropoulos, *et al*. evaluated 2,642 older adults (age 71–80) from the Health Aging and Body Composition Study. The majority of subjects had hypertension and 1/4 reported prevalent vascular disease at baseline. Sodium intake was assessed by food frequency questionnaire at year 2 of the study and events were assessed over a 10-year period. Estimated sodium intake was not significantly associated with mortality, incident cardiovascular disease, or incident HF [72].

Controversy also exists regarding the relationship between sodium intake and cardiovascular events, such as myocardial infarction, which predispose individuals to developing HF. The Trials of Hypertension Prevention I and II studies randomized over 3,000 prehypertensive subjects to usual care vs. non-pharmacological intervention to prevent the onset of hypertension. A total of 1,518 participants were assigned to an intensive dietitian-facilitated program to reduce sodium intake over 18–36 months, with overall reduction in 24 h sodium excretion of approximately 50 mmol/day. Upon 10-year observational follow-up, subjects assigned to the sodium-restriction intervention had 25 % lower risk of cardiovascular events (as a composite of myocardial infarction, coronary revascularization, stroke, and cardiovascular mortality) [73]. Further analysis of the same dataset revealed a linear 17 % increase in risk of cardiovascular events for every 1 g/day increase in sodium excretion, albeit of borderline statistical significance ($p = 0.054$) [74]. These findings have been challenged by a subsequent Cochrane review, including two additional randomized trials [75], which concluded that current data are insufficient to determine if dietary sodium restriction affects cardiovascular morbidity or mortality.

Why do cohort studies have such contradictory results?

Having reviewed several observational studies relevant to understanding the impact of sodium restriction on HF prevention, it is clear that the results are heterogeneous and even at times contradictory. Ideally, outcome-powered randomized controlled trials would fully elucidate the relationship of sodium intake on incident HF. Unfortunately, such trials may be cost-prohibitive, as large sample sizes and prolonged follow-up would be required. Furthermore, the longer the study, the more difficult and resource-intensive it is to sustain long-term differences in sodium intake among study participants. Because of these barriers to performing randomized controlled trials, critical evaluation of the results from observational cohort studies is necessary. In a recent Science Advisory from the American Heart Association evaluating the methodology used in cohort studies linking sodium intake to cardiovascular disease, Cobb, *et al*. recognized an average of 3–4 potential sources of bias in the 26 studies that were evaluated. Many of the studies were not sufficiently powered to detect a significant difference in cardiovascular disease risk. In addition, several methodological factors were identified that could alter the direction of association between sodium intake and cardiovascular disease, including the incidence of HF [76].

Reverse causality is one concern that could alter the direction of an association between sodium intake and cardiovascular disease. This occurs when higher-risk individuals consume less sodium either because they have been instructed to do so by their healthcare team or because their illness leads to decreased overall food consumption. While there have been recent exceptions [3], many observational reports have not adjusted estimated sodium intake for overall energy intake, making overall poor nutritional status a potential confounder. As the overall cardiovascular risk level of the population increases, so does the potential for reverse causality due to malnutrition, previous dietary education, or unmeasured clinical risk factors.

Perhaps, the most important methodological issue to consider is the potential for systematic error or misclassification in sodium intake. Food records or diaries are subjects to inaccurate, biased, or incomplete recall, and typically do not account for salt added during cooking, at the table, or in drinking water. Food frequency questionnaires, which survey habitual intake of commonly consumed foods, do not reflect between-brand differences in nutrient content of the processed foods that constitute an increasing proportion of the Western diet. Measurement of 24 h urinary sodium has long been considered the "gold standard" for estimating dietary sodium intake, although care must be taken to ensure complete collection. However, relying on a single 24 h measurement of any kind may be insufficient, considering that sodium intake varies on a daily basis. Cobb, *et al*. argue that averaging multiple 24 h urinary sodium collections provide the most accurate characterization of an individual's usual sodium intake [76], a conclusion supported by recent longitudinal data collected during periods of carefully controlled and monitored sodium intake [77]. Unfortunately, due to subject burden, few studies, thus, far have been able to assess sodium intake in this fashion.

Conclusions

High dietary sodium intake is associated with several factors that promote the development of HF, including systemic hypertension, ventricular hypertrophy, diastolic dysfunction, vascular stiffness, and endothelial dysfunction. However, dietary sodium restriction may cause potentially detrimental neurohormonal activation. Due in part to methodological limitations, currently available cohort studies have not fully clarified the links between sodium intake and incident HF. Additional research is critically needed to address several key gaps, including determining accurate and reproducible methods of measuring sodium intake and identifying factors which may make specific individuals more vulnerable to developing HF in the setting of high sodium intake.

References available on request Healthcare.India@springer.com

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REVIEW ARTICLE

Olmesartan in the treatment of hypertension in elderly patients: a review of the primary evidence

Massimo Volpe, Giuliano Tocci

Extensive clinical evidence has demonstrated the excellent efficacy and tolerability profile of olmesartan medoxomil (OM) – an angiotensin II receptor blocker AT1 receptor antagonist – including in elderly patients. This article provides an overview of the main recent clinical evidence supporting the use of OM-based therapy in elderly patients with hypertension.

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Hypertension, particularly systolic hypertension, is prevalent in the elderly and increases with advancing age, in part because of age-related endothelial dysfunction and increased arterial stiffness. There is strong evidence from randomized clinical trials that supports the use of antihypertensive treatment for effective and sustained blood pressure (BP) control in older patients to reduce the risk of vascular-related morbidity and mortality, particularly cerebrovascular accidents, including stroke. Furthermore, current evidence and guidelines suggest that all major classes of antihypertensive agents are equally effective in controlling BP and preventing cardiovascular events in older patients. Diuretics are commonly used in elderly patients, but recent outcomes data have raised doubt about their long-term benefits. Renin–angiotensin system inhibitors have a better tolerability profile than diuretics. Extensive clinical evidence has demonstrated the excellent efficacy and tolerability profile of olmesartan medoxomil (OM) – an angiotensin II receptor blocker AT1 receptor antagonist – including in elderly patients. Randomized and observational studies have shown that OM provides effective BP control across the 24 h dosing interval in the elderly. It also has a good tolerability profile, a pharmacokinetic profile unaffected by age and a low propensity for drug interactions. An additional factor is that OM once-daily regimens are simple and straightforward, which can be an important factor in maintaining adherence to therapy in elderly patients. This article provides an overview of the main recent clinical evidence supporting the use of OM-based therapy in elderly patients with hypertension.

Introduction

Hypertension is the most prevalent modifiable risk factor for cardiovascular morbidity and mortality worldwide [1]. Hypertension is common and is known to increase with age, reaching its highest prevalence among individuals aged ≥65 years [2]. At least two thirds of adults aged >65 years in Western countries are affected by hypertension [2]. Age-related endothelial dysfunction and increased arterial stiffness contribute to the increased prevalence of hypertension, particularly systolic hypertension, among elderly individuals [3]. Furthermore, difficult-to-treat or challenging hypertension is common in the elderly, mostly because of the increased use of drugs such as non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, which elevate blood pressure (BP) [4, 5]. Finally, the frequent concomitant presence of clinical conditions or comorbidities, such as chronic kidney disease, obstructive sleep apnoea and renal artery stenosis, may contribute to an increase in BP or exacerbate the detrimental outcomes of hypertension [1, 3, 6].

There is strong evidence supporting the benefit of antihypertensive treatment for effective and sustained (24 h) BP control in older patients. The hypertension in the very elderly trial (HYVET) recently demonstrated the benefits of lowering BP to prespecified targets in the elderly [7]. The recent update of the European guidelines on hypertension recommend drug treatment in elderly hypertensive patients when systolic BP (SBP) is ≥160 mmHg and even when SBP is in the 140–159 mmHg range, if antihypertensive treatment is effective and well tolerated. In patients aged ≤80 years who have SBP ≥160 mmHg, it is now recommended that SBP be reduced to a range of 140–150 mmHg [8].

While the evidence and guidelines are clear, there are many issues complicating the treatment of hypertension in the elderly. These include, among others, associated clinical conditions or comorbidities (such as ischemic heart disease, heart failure, atrial fibrillation, renal impairment and diabetes), drug interactions with concomitant cardiovascular and non-cardiovascular therapies and the adverse effects of those drugs, labile hypertension, orthostatic hypotension, and cognitive decline and dementia [3, 9]. Despite solid evidence of the benefits that can be derived from BP control and regular access to healthcare, elderly patients [the majority of whom have isolated systolic hypertension (ISH)] often present with poorer hypertension control than younger adults [10], particularly older women [11]. Various reasons can be postulated to explain this lack of BP control in elderly individuals, including lack of or delayed titration of an appropriate dosage or relatively low usage of combination therapies, the cost of care, poor adherence to guidelines, inappropriate drug choices, and misperceptions about the benefits/risks of antihypertensive treatment [12].

To further complicate the treatment of hypertension in elderly patients, diurnal patterns of hypertension change with age, with an increased prevalence of non-dipping nocturnal and early-morning hypertension in the elderly [13]. Early-morning or riser hypertension is a pattern associated with the highest cardiovascular risk and is four times as prevalent in patients aged ≥60 years as it is in younger patients [13]. This supports the use of ambulatory BP (AMBP) monitoring during assessment, diagnosis and early treatment to ensure that BP control is maintained throughout the 24 h period [13]. Interestingly, in HYVET, AMBP monitoring identified white-coat hypertension in approximately 50 % of patients aged >80 years. Effective treatment of these patients resulted in an overall reduction in total mortality and cardiovascular events, demonstrating that among the very elderly, those with white-coat hypertension are also likely to benefit from antihypertensive therapy [14].

Current evidence and guidelines suggest that all major classes of antihypertensive agents are equally effective in controlling BP and preventing cardiovascular events in younger or older patients [2, 15, 16, 17]. Several considerations, however, can be made when treating hypertension in elderly individuals. Diuretics, which are commonly used in elderly patients, are recommended as first-line treatment because of their rapid efficacy, particularly in patients with ISH or sustained hypertension (e.g., a non-dipper profile). However, data emerging from large long-term outcomes trials have indicated that thiazide diuretics are associated with adverse metabolic effects and poorer outcomes in specific subgroups of hypertensive patients with metabolic abnormalities (including those with obesity, metabolic syndrome, impaired glucose tolerance and diabetes), mostly when combined with beta-blockers, so that their place as a first-line therapy in the elderly might be reconsidered [18]. Among the other available antihypertensive agents, renin–angiotensin system (RAS) inhibitors, including angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs), have been shown to effectively lower BP levels in both adults and elderly subjects, as well as providing the best tolerability profiles, compared with other antihypertensive drug classes [16, 19]; this is also true in elderly patients [6].

Olmesartan medoxomil (OM) is an ARB that inhibits the action of RAS at the AT1 subtype receptor level [19, 20]. It is eliminated mainly in the urine (35–50 %) and faeces (via the bile) [19, 20]. Oral OM 10–40 mg/day is recommended for the treatment of adult patients with arterial hypertension [16]. Extensive clinical evidence from several large randomized clinical trials [21, 22] and those performed in a clinical practice setting [23] have confirmed the antihypertensive efficacy and good tolerability profile of oral OM in adults, including elderly patients with systolic and diastolic hypertension, or ISH [20]. OM is also known to provide sustained BP control across the 24 h dosing interval, including the high-risk morning/awakening period [24].

This article reviews recent clinical evidence and discusses the role of OM in the treatment of hypertension in elderly patients.

Extensive clinical evidence has confirmed the antihypertensive efficacy and good tolerability profile of oral olmesartan medoxomil in adults, including elderly patients with systolic and diastolic hypertension, or isolated systolic hypertension.

Methods

Key studies for inclusion in this review were identified by a MEDLINE search, based on several interrelated queries using the search terms 'olmesartan' AND 'elderly'. Restrictions in terms of the year of publication were not applied, but only studies published in the English language were considered. Because of the narrative approach of this review, the resulting articles were chosen according to their relevance, as judged by the authors. The search results were then supplemented by manually browsing the reference list of identified articles, and by

including other documents suggested by the authors' experience. Both subgroup analyses and studies specifically conducted in elderly patients in which OM was administered either alone or in combination with another antihypertensive agent, at any dosage, were considered.

Pharmacokinetics of olmesartan in the elderly

In elderly hypertensive patients, and in patients with renal and hepatic dysfunction, OM was rapidly absorbed and converted to olmesartan, no OM itself was detected in plasma, and steady state was reached within the first few days after oral dosing [25]. After administration of OM 80 mg once daily in elderly hypertensive patients (aged 65–75 years) and 10 mg daily in very elderly patients (aged ≥75 years), the steady-state peak serum concentration (C_{max}) and area under the curve from 0 to 24 h (AUC_{0-24h}) values were up to 44 % higher than those in young patients (aged <46 years). The steady-state elimination half-life values were also greater in elderly patients (12.8 vs 10.6 h at day 10) and in very elderly patients (16.5 vs 12.3 h at day 14) compared with those in younger patients. Since the increased plasma concentrations (C_{max} and AUC_{0-24h}) after OM 80 mg daily in elderly and very elderly patients, and in those with mild and moderate renal and hepatic impairment, were several-fold lower than plasma concentrations observed in other studies, and the regimen was well tolerated, a dosing adjustment in these groups is not considered necessary [20]. In patients with severe renal impairment, however, consideration should be given to a lower starting dose, and it is recommended that the daily dose should not exceed 20 mg daily (compared with 40 mg daily in the general patient population) [25].

In addition to its favourable pharmacokinetic profile, OM is not metabolized by the cytochrome P450 enzyme system, thus, it has a low propensity for metabolic drug interactions. This characteristic is likely to be important in the elderly, who are particularly likely to be receiving multiple drug therapies [26].

Clinical efficacy of olmesartan in the elderly

Strong clinical evidence of the efficacy of OM-based therapy in the elderly is found mainly in the following subgroup analyses of large randomized controlled trials.

Subgroup/post hoc analyses of data from controlled clinical trials

Overall, OM, either alone or in combination with a thiazide diuretic, such as hydrochlorothiazide (HCTZ), and/or a calcium channel blocker (CCB), such as amlodipine, provides similar control of hypertension in younger adults and elderly patients, according to results from several subgroup/post hoc analyses of clinical trial data. Many studies have evaluated the use of an OM-based stepped titration algorithm as would be used in the clinical setting.

Olmesartan medoxomil, either alone or in combination with a thiazide diuretic, such as hydrochlorothiazide, and/or a calcium channel blocker, such as amlodipine, provides similar control of hypertension in younger adults and elderly patients, according to results from several subgroup/post hoc analyses of clinical trial data.

In a prespecified secondary analysis of a 12-week, open-label, single-arm, dose-titration study, Neutel, *et al.* [27] evaluated the BP-lowering efficacy and safety of an OM/HCTZ-based titration regimen in patients aged ≥65 years with hypertension. Subgroups were stratified by age (≥65 to ≤75 or >75 years), gender (male or female) and race (Black or non-Black). Baseline and week-12 AMBP monitoring data were available for 84 % of patients who entered the active treatment phase [27]. Changes from baseline in mean 24 h AMBP at week 12 were significant ($p < 0.0001$) versus baseline in patients aged ≥65 to ≤75 years ($n = 128$) and >75 years ($n = 48$), respectively [27]. Clinically significant AMBP reductions were also observed during the daytime, night-time and the last 6, 4 and 2 h of the dosing interval in all subgroups [27]. Changes from baseline at week 12 in mean seated BP (SeBP) were similar to 24 h AMBP changes reported previously. At week 12, the proportion of patients achieving the 24 h AMBP target of <130/80 mmHg ranged from 67.5 to 77.4 %, and achievement of the SeBP goal of <140/90 mmHg ranged from 60.7 to 68.8 % across the subgroups. Overall, similar results with this treatment regimen were obtained in an age-stratified subgroup analysis of a study conducted in diabetic patients [28]. BP reductions were significant and similar among age subgroups, and following dose titration to OM/HCTZ 40/25 mg/day, similar proportions of patients in the age subgroups achieved an AMBP target of <130/80 mmHg.

Schmieder and Böhm [29] investigated the efficacy of OM/amlodipine in age-, severity- and gender-based subgroups of patients with moderate-to-severe hypertension uncontrolled by amlodipine monotherapy. Patients with uncontrolled BP after 8 weeks of amlodipine 5 mg monotherapy ($n = 755$) were randomized to continue amlodipine 5 mg or to receive OM (10–40 mg) plus amlodipine 5 mg for 8 weeks, up-titrated to OM/amlodipine 20/5, 40/5 or 40/10 mg as required. The antihypertensive effects of OM/amlodipine were similar in patients aged <65 and ≥65 years of age.

Oparil, *et al.* [30] presented the results of a subgroup analysis of a 44-week, open-label extension study in which the efficacy and safety of the combination of amlodipine plus OM with and without the addition of HCTZ were investigated in patients aged ≥65 and <65 years. After an 8-week, double-blind, placebo-controlled phase, patients who initiated therapy with OM/amlodipine 40/5 mg/day were titrated to OM/amlodipine 40/10 mg/day, with the addition of HCTZ 12.5 or 25 mg as required if the BP goal was not achieved (<140/90 mmHg). At week 44, the BP goal was achieved in 61.0 and 68.1 % of those aged ≥65 and <65 years, respectively.

In a prespecified secondary analysis of a randomized controlled trial, Chrysant, *et al.* [31] compared the efficacy of amlodipine (10 mg/day), OM (40 mg/day), a combination of the two, or placebo in patients aged >65 years over 8 weeks. All active treatments resulted in significant BP reductions from baseline ($p < 0.05$). The antihypertensive effect of the amlodipine plus OM combination was generally greater than with amlodipine or OM monotherapies, and more patients receiving combination therapy achieved the BP goal.

Lastly, Oparil and Pimenta [32] performed a prespecified subgroup analysis of a 12-week, randomized, placebo-controlled, titrate-to-goal study in patients with hypertension, stratifying patients into treatment groups according to age, gender or race. After 12 weeks, OM-based therapy

significantly reduced BP from baseline in patients aged <65 or ≥65 years compared with placebo. The differences in the BP-lowering efficacy of OM-based therapy between age subgroups were not clinically significant.

Observational studies of olmesartan

The aforementioned findings from subgroup analyses of clinical trials were confirmed in studies conducted in the clinical practice setting.

Bramlage, *et al.* [33] conducted a multicentre, noninterventional, noncontrolled observational study of 8,241 hypertensive patients (mean age 62.8 ± 11.8 years) seen by 2,187 physicians in daily practice. BP reduction, comorbid disease, pharmacotherapy and tolerability were documented over a 12- to 18-week observation period. In total, 51.3 % of patients received OM/amlodipine 20/5 mg, 30.6 % received 40/5 mg and 17.9 % received 40/10 mg at baseline, mostly because of lack of efficacy of prior antihypertensive therapy (73.8 %). BP at baseline was 161.8/93.6 mmHg (39.8 % had grade 2 hypertension), and the observed BP reduction was 29.0/13.5 mmHg ($p < 0.0001$), with a significant correlation between baseline BP and BP reduction. BP reduction appeared to be dependent on dose and prior antihypertensive therapy, but not on age, gender, body mass index, duration of hypertension or presence of diabetes. At the final visit, 69.4 % of patients were controlled (<140/90 mmHg), compared with 4.3 % at baseline.

Ram, *et al.* [34] performed a retrospective analysis comparing the efficacy of OM, losartan, valsartan and irbesartan in patients with hypertension ($n = 73,012$) over 13 months. Overall, 40.8 % of patients were aged >65 years; the proportion of elderly patients was slightly lower in the OM group than in the losartan, valsartan and irbesartan groups (36.1 vs 42.6, 41.2 and 42.1 %). After adjustment for baseline BP, starting dose, year, age, gender, race, body mass index, comorbid conditions and concomitant medications, all ARBs provided sustained BP reductions, but there were significant differences in the extent of BP reduction. After adjustment for all covariates, the overall BP reductions were greater with OM than with losartan, valsartan and irbesartan (differences vs OM: 1.88/0.86, 1.21/0.52 and 0.89/0.51 mmHg, respectively) and the differences were even greater for monotherapy (2.43/1.16, 2.18/0.93 and 1.44/0.91 mmHg, respectively; all $p < 0.0001$). The adjusted odds ratios of the likelihood of attaining the BP goals defined in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7 [34]) were 0.76, 0.86 and 0.91 ($p < 0.05$) for losartan, valsartan and irbesartan, respectively, compared with OM [34].

The results of a recent meta-analysis of 22 randomized controlled trials comparing olmesartan medoxomil with other angiotensin II receptor blockers in terms of BP reduction and control showed that olmesartan medoxomil provided greater reductions in diastolic and systolic BP than losartan and greater reductions in systolic BP than valsartan.

Meta-analyses comparing olmesartan with other angiotensin receptor blockers

The results of a recent meta-analysis of 22 randomized controlled trials ($n = 4,892$) comparing OM with other ARBs in terms of BP reduction and control [35] showed that OM provided greater reductions in DBP and SBP than losartan and greater reductions in SBP than valsartan [random-effects model, weighted mean differences: DBP 1.61 (95 % confidence interval [CI] 0.59–2.62); SBP 3.19 (95 % CI 0.46–5.92)] [35]. All agents (OM, losartan, valsartan, candesartan and irbesartan) had similar BP response rates and incidences of adverse events.

Comparative trials conducted in elderly patients

Several comparative studies specifically conducted in elderly or very elderly patients have demonstrated consistently that olmesartan medoxomil – either alone or in combination with HCTZ, the ACE-inhibitor ramipril, amlodipine or a CCB-provides effective control of hypertension in this population that is comparable to or greater than the benefit associated with other

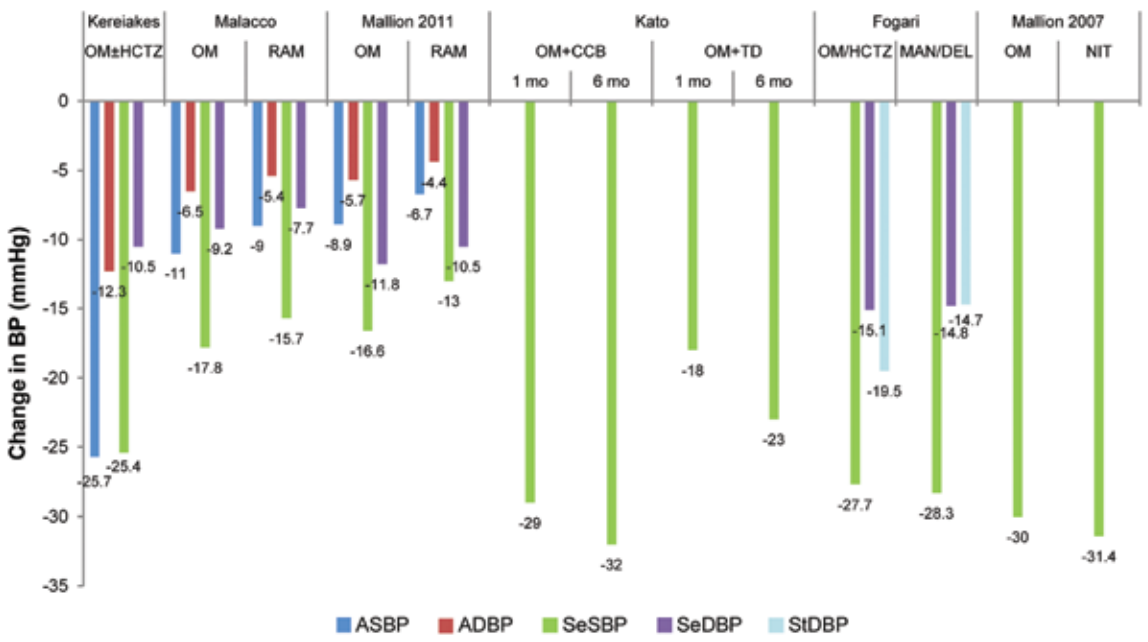

Fig. 1: Reductions in blood pressure following olmesartan medoxomil (OM) administration in elderly patients in different studies [19, 24, 36, 37, 38, 39]. *ADBP* ambulatory diastolic blood pressure, *ASBP* ambulatory systolic blood pressure, BP blood pressure, *CCB* calcium channel blocker, *DEL* delapril, *HCTZ* hydrochlorothiazide, *MAN* manidipine, *NIT* nitrendipine, *RAM* ramipril, *SeDBP* seated cuff diastolic blood pressure, *SeSBP* seated cuff systolic blood pressure, *StDBP* standing cuff diastolic blood pressure, *TD* thiazide diuretic.

Table 1: Summary of randomized controlled clinical trials of olmesartan medoxomil specifically conducted in elderly patients with hypertension [19, 24, 36, 37, 38, 39].

Reference	Design (duration)	Treatments	Patients (n)	Age range (years [mean ± SD])	Primary efficacy endpoint	Results [95 % CIs]
Kereiakes, *et al.* [24]	R, O, MC, BEP (12 weeks)	OM 20/40 mg/day ± HCTZ 12.5/25 mg/day	176; newly diagnosed/uncontrolled HT (SeSBP/SeDBP ≥140/90 mmHg)	65–86 [71.9 ± 5.2]	Change in mean 24 h ABP at week 12	Reduction in mean 24 h AMBP: 25.7/12.3 mmHg (n = 150); reduction in mean SeBP: 25.4/10.5 mmHg (n = 176), all $p < 0.00001$ vs BL; mean AMBP goals achieved in 88.7, 82.7, 73.3, 56.7 and 44.0 % (<140/90, <135/85, <130/80, <125/75 and <120/80 mmHg)
Malacco, *et al.* [19]	R, DB, PG (12 weeks)	OM 10 mg/day vs RAM 2.5 mg/day	1,102; treated or untreated HT (AMBP n = 630)	65–89 [72 ± 5]	Changes in SeSBP and SeDBP at week 12	Reductions in SBP and DBP: OM 17.8 mmHg (95 % CI 16.8–18.9) and 9.2 mmHg (95 % CI 8.6–9.8) vs RAM 15.7 mmHg (95 % CI 14.7–16.8) and 7.7 mmHg (95 % CI 7.1–8.3), $p < 0.01$; BP normalization rate: OM 52.6 % vs RAM 46.0 %, $p < 0.05$; reduction in ABP: OM SBP 11.0 mmHg (95 % CI 9.9–12.2) and DBP 6.5 mmHg (95 % CI 5.8–7.2) vs RAM 9.0 mmHg (95 % CI 7.9–10.2) and 5.4 mmHg (95 % CI 4.7–6.1), $p < 0.05$
Mallion, *et al.* [39]	R, DB, MC, PG (12 weeks)	OM 10 mg/day, RAM 2.5 mg/day	351; HT (SeSBP/DBP 140–179/90–109 mmHg) (AMBP n = 85)	65–89 [OM 72 ± 5; RAM 71 ± 5]	Rates of BP goal achievement (BP goals: <140/90 mmHg in nondiabetic patients and <130/80 mmHg in diabetic patients)	BP goal achievement rate: OLM 38.8 % vs RAM 26.3 %, $p = 0.013$; reduction in mean SeSBP: OM 16.6 mmHg (95 % CI 14.0–19.2) vs RAM 13.0 mmHg (95 % CI 10.4–15.6), $p = 0.206$; reduction in mean SeDBP: 11.8 mmHg (95 % CI 10.3–13.3) vs 10.5 mmHg (95 % CI 9.0–12.0), $p = 0.351$; reduction in 24 h ABP: OM SBP 8.9 mmHg (95 % CI 8.1–9.8) and DBP 5.7 mmHg (95 % CI 5.1–6.3) vs RAM 6.7 mmHg (95 % CI 5.6–7.9) and 4.4 mmHg (95 % CI 3.7–5.1) mmHg, $p = 0.01$
Kato, *et al.* [37]	R, O, MC (6 months)	OM + D-CCB (AZL, AML or BEN) vs OM + TD (TCM or IND) (mean OM doses: 22.1 mg/day with CCB and 21.2 mg/day with TD)	58; HT >140/90 mmHg on treatment or >160/100 mmHg if treatment naive	65–85 [+CCB 72.6 ± 6.1; +TD 73.3 ± 5.9]	Changes in mean SBP at 1 and 6 months	Reductions in SBP at 1 and 6 months: OM + CCB 29 and 32 mmHg vs OM + TD 18 and 23 mmHg
Fogari, *et al.* [36]	R, O, BEP (48 weeks)	OM 20 mg/day/HCTZ 12.5 mg/day vs MAN 10 mg/day/DEL 30 mg/day	158; essential HT (SeSBP/DBP 130–179/80–99 mmHg) with T2DM	66–74 [MAN/DEL 69.5 ± 3.2; OM/HCTZ 70.2 ± 3.5]	Changes in SeSBP/DBP at week 48	Reduction in SeSBP 27.7 and 28.3 mmHg (both $p < 0.001$) and reduction in SeDBP 15.1 and 14.8 mmHg with MAN/DEL and OM/HCTZ, respectively (both $p < 0.01$); no difference between the two treatments; reduction in standing DBP greater with OM/HCTZ: 19.5 mmHg vs MAN/DEL 14.7 mmHg ($p < 0.05$)
Mallion, *et al.* [38]	R, DB, stepped (24 weeks)	OM 20/40 mg/day vs NIT 10/20 mg bid (both + HCTZ 12.5/25 mg/day as required)	382; ISH	65–94, split into 65–74 and ≥75 groups [OM 74.0 ± 6.1; NIT 73.5 ± 5.8]	Change in SeSBP at week 12	Overall reduction in SeSBP: OM 30 mmHg vs NIT 31.4 mmHg; SBP at week 24 and DBP at weeks 12 and 24 were significantly reduced from BL but no differences between treatment groups; no significant effect of age

AMBP ambulatory blood pressure, *AML* amlodipine, *AZL* azelnidipine, *BEN* benidipine, *BEP* blinded endpoint study, *bid* twice daily, *BL* baseline, *CCB* calcium channel blocker, *CI* confidence interval, *DB* double blind, *DBP* diastolic blood pressure, *D-CCB* dihydropyridine calcium channel blocker, *DEL* delapril, *HCTZ* hydrochlorothiazide, *HT* hypertension, *IND* indapamide, *ISH* isolated systolic hypertension, *MAN* manidipine, *MC* multicentre, *NIT* nitrendipine, *O* open, *OM* olmesartan medoxomil, *PG* parallel group, *R* randomized, *RAM* ramipril, *SBP* systolic blood pressure, *SD* standard deviation, *SeBP* seated blood pressure, *SeSBP* seated cuff systolic blood pressure, *SeDBP* seated cuff diastolic blood pressure, *T2DM* type 2 diabetes mellitus, *TCM* trichlormethiazide, *TD* thiazide diuretic

antihypertensive regimens [19, 24, 36, 37, 38, 39]. A summary of these six studies and the key efficacy outcomes are shown in Table 1. Changes in mean BP from baseline are shown in Fig. 1.

Randomized Controlled Trials

Kereiakes, *et al.* [24] examined the effects of OM with or without HCTZ on mean 24 h AMBP, mean SeBP and SeBP goal achievement in elderly patients with hypertension. After a 2- to 3-week placebo run-in period, patients received OM 20 mg, up-titrated to OM 40 mg, and then added HCTZ 12.5–25 mg in a stepwise manner at 3-week intervals if SeBP remained ≥120/70 mmHg. At the end of the study, both 24 h AMBP (n = 150) and SeBP (n = 176) had decreased significantly compared with baseline ($p < 0.00001$) (Fig. 1).

Malacco, *et al.* [19] compared the efficacy and safety of OM and ramipril in elderly patients with essential arterial hypertension. After a 2-week placebo washout, 1,102 treated or untreated elderly hypertensive patients aged 65–89 years were randomized to 12-week double-blind treatment with OM 10 mg or ramipril 2.5 mg once daily, doubled after 2 and 6 weeks in non-normalized individuals (nondiabetic BP <140/90 mmHg and diabetic <130/80 mmHg). In the intention-to-treat population (542 and 539 patients receiving OM and ramipril, respectively), 12 weeks of OM treatment resulted in significantly greater

baseline-adjusted seated cuff SBP and DBP (SeSBP and SeDBP) reductions ($p < 0.01$) than ramipril (Fig. 1). The BP normalization rate was also greater with OM (52.6 vs 46.0 %, $p < 0.05$). In patients with valid AMBP recordings ($n = 318$ and 312 receiving OM and ramipril, respectively), the reduction in 24 h average BP was greater with OM ($p < 0.05$) (Fig. 1); this was particularly evident in the last 6 h of the dosing interval (better 24 h BP control with OM confirmed by higher smoothness indices).

A similar study by Mallion, *et al.* [39] compared the efficacy and safety of OM and ramipril in elderly patients with essential arterial hypertension, and reached similar conclusions to those of Malacco, *et al.* [19]. After a 2-week placebo washout, 351 elderly hypertensive patients aged 65–89 years (office SeDBP 90–109 mmHg, SeSBP 140–179 mmHg) were randomized to 12-week double-blind treatment with OM 10 mg or ramipril 2.5 mg once daily, doubled at weeks 2 and 6 in non-normalized subjects (BP <140/90 mmHg for non-diabetic subjects and <130/80 mmHg for diabetic subjects). At week 12, BP control rates in the intention-to-treat population were significantly greater with OM (38.8 vs 26.3 %, $p = 0.013$). The baseline-adjusted mean office SeBP reductions at the final visit were similar in the different treatment groups (Fig. 1). However, in patients with valid AMBP recordings, the reduction in 24 h average BP was significantly greater with OM ($p < 0.01$) (Fig. 1), and this was particularly evident in the last 4 h of the dosing interval.

Kato, *et al.* [37] compared the effects of combination therapies, including OM and either a CCB or a thiazide diuretic, in elderly patients with hypertension. A total of 65 patients aged 65–85 years, with BP ≥140/90 mmHg for those taking antihypertensive medication or ≥160/100 mmHg for those not on medication, were randomly assigned to OM plus a dihydropyridine CCB or OM plus a thiazide diuretic; 58 patients completed 6 months of treatment. SBP and DBP were significantly reduced from baseline during the treatment period in both groups (Fig. 1), but reductions in SBP at 1 and 6 months were significantly greater ($p < 0.05$) in the CCB combination group than in the diuretic group.

Fogari, *et al.* [36] compared the combination treatments of manidipine/delapril and OM/HCTZ in elderly diabetic hypertensive patients. After a 4-week placebo period, 158 hypertensive patients with type 2 diabetes (age range 66–74 years) were randomized to receive combination treatment with manidipine 10 mg plus delapril 30 mg or OM 20 mg plus HCTZ 12.5 mg for 48 weeks in a prospective, parallel-arm trial. After 12 weeks, manidipine or HCTZ was doubled in nonresponders (SBP ≥130 mmHg and/or DBP ≥80 mmHg). Both combinations significantly reduced SeSBP ($p < 0.001$) and SeDBP ($p < 0.01$) from baseline, with no difference between the two treatments. Standing DBP was more markedly reduced by OM/HCTZ ($p < 0.001$) than by manidipine/delapril ($p < 0.05$ vs OM/HCTZ) (Fig. 1).

Mallion, *et al.* [38] compared the antihypertensive efficacy of OM with that of the dihydropyridine CCB nitrendipine in elderly (aged 65–74 years) and very elderly (aged ≥75 years) male and female patients with ISH. Patients were randomized to 24 weeks of treatment with either OM 20 mg daily ($n = 256$) or nitrendipine 20 mg twice daily ($n = 126$), with a possible dose increase (to 40 mg daily) and addition of HCTZ 12.5 or 25 mg daily if required. With regard to reductions in mean SeSBP after 12 weeks of treatment, the two treatments were similar (Fig. 1). No significant difference between the treatment groups was observed, and non-inferiority of OM to nitrendipine was demonstrated. Reductions in mean sitting and standing SBP and DBP up to week 24 were also similar with both treatments. BP goal attainment rates (SeSBP ≤135 mmHg) increased consecutively and were greater with OM (62.5 %) than with nitrendipine (56.0 %) at week 24 (not significant).

Non-randomized Observational Trials/ Retrospective Analyses

Saito, *et al.* [40] assessed the efficacy and safety of OM in 550 elderly Japanese hypertensive patients who were followed for 24 weeks in daily clinical practice. Patients were given OM alone or in combination with other antihypertensive drugs at the discretion of the investigators. After 24 weeks of treatment, SBP and DPB significantly decreased from baseline ($p < 0.0001$). When patients were classified as either young-old (65–74 years) or older-old (≥75 years), with either ISH or systolic–diastolic hypertension, the reduction of DBP in ISH patients was significantly smaller than that in systolic–diastolic hypertension patients (5.0 vs 15.2 mmHg, $p < 0.0001$), indicating that OM did not cause excessive reduction of DBP in ISH patients. Treatment was well tolerated in all groups. The authors concluded that the medication was safe and effective in reducing BP levels in ISH patients aged ≥75 years, as well as in other elderly hypertensive patients.

In a recently published study by Omboni, *et al.* [41], the antihypertensive effects of OM and ramipril on 24 h AMBP monitoring in elderly hypertensive patients were assessed by pooled data analysis of two studies with identical designs (one Italian, one European). After a 2-week placebo washout, 1,453 elderly hypertensive patients (aged 65–89 years; office SeDBP 90–109 mmHg and/or office SeSBP 140–179 mmHg) were randomized to a 12-week double-blind treatment period with OM 10 mg or ramipril 2.5 mg once daily, up-titrated (20 and 40 mg OM; 5 and 10 mg ramipril) after 2 and 6 weeks in patients without normalized office BP. In 715 patients with valid baseline and end-of-treatment recordings, the baseline-adjusted 24 h SBP and DBP reductions were greater with OM ($n = 356$) than with ramipril ($n = 359$) [between-treatment differences: SBP reduction 2.2 mmHg (95 % CI 0.6–3.8), $p = 0.006$; DBP reduction 1.3 mmHg (95 % CI 0.3–2.2), $p = 0.009$]. OM showed larger BP reductions in the last 6 h of the dosing interval and higher smoothness indices than ramipril. OM reduced the SBP morning rise [by 2.8 mmHg (95 % CI 0.8–4.9)], whereas ramipril did not [SBP increased by 1.5 mmHg (95 % CI –0.6 to +3.6), $p = 0.004$ between treatments]. Five hundred and eighty-two patients with sustained hypertension (office and 24 h ambulatory hypertension) showed the largest antihypertensive effect, with between-treatment differences still in favour of OM [SBP reduction 2.1 mmHg (95 % CI 0.4–3.9), $p = 0.019$; DBP reduction 1.2 mmHg (95 % CI 0.1–2.3), $p = 0.032$].

Two further post hoc analyses of pooled data from the same two randomized, double-blind, parallel-group, multicentre studies that were analyzed in the aforementioned study by Omboni, *et al.* [41] also compared the head-to-head antihypertensive efficacy and safety of OM and ramipril in elderly patients on the basis of renal function and the presence or absence of metabolic syndrome [42, 43]. In the renal function pooled analysis by Malacco, *et al.* [42, 43], the comparative efficacy of OM and ramipril was evaluated in elderly patients with a normal or increased estimated glomerular filtration rate (eGFR; ≥90 mL/min/1.73 m^2; $n = 181$), mild eGFR reduction (60–90 mL/

min/1.73 m^2; n = 840), or moderate-to-severe eGFR reduction (<60 mL/min/1.73 m^2; n = 405) [43]. Compared with ramipril, OM was associated with superior baseline-adjusted office BP reductions in patients with normal or increased eGFR [between-treatment differences: SBP reduction 5.0 mmHg (95 % CI 0.9–9.1), p = 0.018; DBP reduction 2.7 mmHg (95 % CI 0.6–4.8), p = 0.011] and in patients with mildly reduced eGFR [SBP reduction 1.6 mmHg (95 % CI 0.2–3.5), p = 0.080; DBP reduction 1.2 mmHg (95 % CI 0.2–2.3), p = 0.022], but similar reductions were seen in those with moderate-to-severe eGFR reductions [SBP reduction 1.9 mmHg (95 % CI 0.9–4.6), not significant; DBP reduction 0.8 mmHg (95 % CI −0.7 to 2.3), not significant]. BP normalization rates after 12 weeks of treatment were also greater with OM than with ramipril in patients with normal or increased eGFR (46.1 vs 23.9 %, p = 0.002) and mildly reduced eGFR (49.9 vs 42.7 %, p = 0.037) but were comparable in those with moderate-to-severe eGFR reduction (49.5 vs 46.3 %; not significant). In patients with valid baseline and end-of-treatment AMBP recordings, the baseline-adjusted 24 h SBP and DBP reductions were greater with OM than with ramipril in patients with mildly reduced eGFR [between-treatment differences: SBP reduction 2.5 mmHg (95 % CI 0.5–4.5), p = 0.015; DBP reduction 1.3 mmHg (95 % CI 0.1–2.6), p = 0.041]; no significant treatment differences were seen in patients with normal or increased eGFR, or moderate-to-severe eGFR reduction.

In the metabolic syndrome pooled analysis by Omboni, *et al.* [42], the antihypertensive efficacy of OM and ramipril were compared in elderly patients with metabolic syndrome (n = 735) or without metabolic syndrome (n = 691), which was defined as patients with central obesity and two or more of the following risk factors: SBP ≥130 mmHg or DBP ≥85 mmHg (or treatment for previously diagnosed hypertension); raised triglyceride levels; reduced high-density lipoprotein cholesterol levels; and raised fasting plasma glucose levels. At 12 weeks, OM was associated with greater baseline-adjusted office BP reductions than ramipril in patients with metabolic syndrome [between-treatment differences: SBP reduction 2.3 mmHg (95 % CI 0.3–4.4), p = 0.026; DBP reduction 1.2 mmHg (95 % CI 0.1–2.3), p = 0.039] and in patients without metabolic syndrome [SBP reduction 2.0 mmHg (95 % CI 0.1–4.0), p = 0.046; DBP reduction 1.4 mmHg (95 % CI 0.2–2.5), p = 0.020]. After 12 weeks of treatment, BP normalization rates were also greater with OM than with ramipril in patients with metabolic syndrome (46.0 vs 35.8 %, p = 0.005), but this significance was lost in patients without metabolic syndrome (52.9 vs 47.0 %; not significant). In patients with valid baseline and end-of-treatment AMBP recordings, baseline-adjusted reductions in SBP and DBP during the 24 h, daytime, night-time, and the last 6 h of the dosing period tended to be greater with OM than with ramipril.

Olmesartan medoxomil provides a convenient, effective and well tolerated option for long-term antihypertensive therapy in elderly patients.

The findings collected in dedicated, well-designed clinical trials were largely confirmed in a large clinical practice study [23]. The authors of that study performed a pooled analysis of 20 post-authorization surveys of OM involving 156,682 hypertensive patients. OM was used as monotherapy or in combination with other antihypertensive drugs such as HCTZ. In all, 43.8 % of patients received OM monotherapy, 29 % received OM with HCTZ and 27.2 % received OM in combination with other antihypertensive agents. Approximately 90 % of patients were responders. BP targets were achieved in 52.8 and 35.7 % of patients without risk factors and in the overall cohort, respectively, but only in 8.1 and 27.5 % of patients with renal dysfunction or those taking NSAIDs, respectively.

Benefits beyond blood pressure lowering

The results of a small study suggested that OM may improve cerebrovascular circulation, in addition to its BP-lowering effect [44]. Ten elderly subjects with first- or second-degree essential hypertension (mean age 70.5 years) underWen,t brain single-photon emission tomography scanning with (99 m) Tc-ethyl cysteinate dimer before and after a 24-week course of OM. Mean SBP was 156.2 mmHg, and mean DBP was 89.1 mmHg. No subject had any abnormalities on neurological examination or a previous history of stroke or cardiovascular disease. Before OM administration, the hypertensive subjects had approximately 15 % less whole brain cerebral blood flow than age-matched normotensive controls. Regional cerebral blood flow was decreased by 11–20 % in the frontal, parietal, temporal and posterior lobes. OM treatment significantly decreased SBP to 130.4 mmHg (p < 0.001) and DBP to 78.2 mmHg (p < 0.001). After 24 weeks of OM treatment, cerebral blood flow in the whole brain and regional cerebral blood flow in the frontal, parietal and temporal lobes were similar to those in control subjects.

Safety of olmesartan in the elderly

As with other ARBs, the overall effectiveness of OM is established by its tolerability and compliance. Safety and tolerability are particularly important in elderly patients. Elderly patients are, in fact, more likely to have some degree of renal and hepatic impairment, which may affect the pharmacokinetics of drugs, and, therefore, dosing adjustment may need to be considered.

A summary of the key safety outcomes from the randomized controlled trials of OM in the elderly is shown in Table 2. In general, OM is well tolerated in the elderly. In clinical trials in elderly patients with hypertension, the most commonly reported drug-related treatment-emergent adverse events were dizziness, headache, gastrointestinal-related effects and hypotension.

There is some evidence that OM is renoprotective. In the study by Kato, *et al.* [37], OM in combination with a CCB did not affect serum creatinine levels or the eGFR, whereas OM plus a thiazide diuretic was associated with elevations in serum creatinine and eGFR, as well as a reduction in high-density lipoprotein cholesterol (all p < 0.05).

One study, that of Fogari, *et al.*[36], in elderly patients with hypertension and diabetes, demonstrated that the OM/HCTZ combination was associated with some adverse metabolic effects, such as increased glycosylated haemoglobin (Hb_{A1c}), elevated uric acid, and triglyceride levels, as well as a reduction in serum potassium and high-density lipoprotein cholesterol levels. In contrast, no changes in these metabolic parameters were observed with the CCB/ACE-inhibitor combination. These findings suggest that the OM/HCTZ combination

Table 2: Key safety data from clinical trials [19, 24, 36, 37, 38, 39].

Reference	Design (duration)	Treatments	Patients (n)	Age range (years [mean ± SD])	DR-TEAEs (% of patients)	Most common DR-TEAEs and other tolerability results
Kereiakes, *et al.* [24]	R, O, MC, BEP (12 weeks)	OM 20/40 mg/day ± HCTZ 12.5/25 mg/day	176; newly diagnosed/ uncontrolled HT (SeSBP/SeDBP ≥140/90 mmHg)	65–86 [71.9 ± 5.2]	11.8 %	Dizziness (3.4 %), hypotension (2.2 %), headache (1.1 %)
Malacco, *et al.* [19]	R, DB, PG (12 weeks)	OM 10 mg/day vs RAM 2.5 mg/day	1,102; treated or untreated HT (AMBP n = 630)	65–89 [72 ± 5]	3.6 % OM, 3.6 % RAM	Cough (RAM 13 vs OM 2 episodes), dizziness or vertigo, asthenia, hypertensive crisis or hypotension
Mallion, *et al.* [39]	R, DB, MC, PG (12 weeks)	OM 10 mg/day, RAM 2.5 mg/day	351; HT (SeSBP/ SeDBP 140–179/90–109 mmHg) (AMBP n = 85)	65–89 [OM 72 ± 5; RAM 71 ± 5]	4.0 % OM, 4.5 % RAM	Cough (only with RAM), dizziness, headache and GI side-effects (diarrhoea, nausea, stomach pain)
Kato, *et al.* [37]	R, O, MC (6 months)	OM + D-CCB (AZL, AML or BEN) vs OM + TD (TCM or IND) (mean OM doses: 22.1 mg/ day with CCB and 21.2 mg/day with TD)	58; HT >140/90 mmHg on treatment or >160/100 mmHg if treatment naive	65–85 [+CCB 72.6 ± 6.1; +TD 73.3 ± 5.9]	NR	Cr and eGFR unchanged with OM + CCB but Cr elevated and eGFR and HDL-C reduced with OM + TD (all $p < 0.05$)
Fogari, *et al.* [36]	R, O, BEP (48 weeks)	OM 20 mg/day/ HCTZ 12.5 mg/ day vs MAN 10 mg/day/DEL 30 mg/day	158; essential HT (SeSBP/SeDBP 130–179/80–99 mmHg) with T2DM	66–74 [MAN/DEL 69.5 ± 3.2; OM/ HCTZ 70.2 ± 3.5]	NR	No changes in metabolic parameters with MAN/DEL; increased Hb_{A1c} (+0.7 %, $p < 0.05$), uric acid (+0.4 mg/ dL, $p < 0.05$) and TG (+41.3 mg/dL, $p < 0.05$) and decreased serum K+ (−0.3 mmol/L, $p < 0.05$) and HDL-C (−3.4 mg/dL, $p < 0.05$) with OM/HCTZ
Mallion, *et al.* [38]	R, DB, stepped (24 weeks)	OM 20/40 mg/day vs NIT 10/20 mg bid (both + HCTZ as required 12.5/25 mg/day)	382; ISH	65–94, split into 65–74 and ≥75 groups [OM 74.0 ± 6.1; NIT 73.5 ± 5.8]	Any AE: OM 38.7 %; NIT 45.2 %	Headache, peripheral oedema, dizziness, nasopharyngitis and vertigo

AE adverse event, *AMBP* ambulatory blood pressure, *AML* amlodipine, *AZL* azelnidipine, *BEN* benidipine, *BEP* blinded endpoint study, *bid* twice daily, *CCB* calcium channel blocker, *Cr* serum creatinine, *DB* double blind, *D-CCB* dihydropyridine calcium channel blocker, *DEL* delapril, *DR-TEAE* drug-related treatment-emergent adverse event, *eGFR* estimated glomerular filtration rate, *GI* gastrointestinal, *HCTZ* hydrochlorothiazide, *HDL-C* high-density lipoprotein cholesterol, Hb_{A1c} glycosylated haemoglobin, *HT* hypertension, *IND* indapamide, *ISH* isolated systolic hypertension, *K+* potassium, *MAN* manidipine, *MC* multicentre, *NIT* nitrendipine, *NR* not reported, *O* open, *OM* olmesartan medoxomil, *PG* parallel group, *R* randomized, *RAM* ramipril, *SD* standard deviation, *SeSBP* seated cuff systolic blood pressure, *SeDBP* seated cuff diastolic blood pressure, *T2DM* type 2 diabetes mellitus, *TCM* trichlormethiazide, *TD* thiazide diuretic, *TG* triglycerides.

may not be the best antihypertensive option in elderly patients with diabetes.

In the large observational analysis performed by Scholze, *et al.* [23], the frequency of drug-related adverse events was 0.4 %, and tolerability was not affected by the dose, presence of comorbidities or age. Adverse events were reported in 0.3 % of the ≥65-year age group and 0.2 % of the <65-year age group. The most frequently reported adverse events were gastrointestinal disorders (nausea, diarrhoea, abdominal pain and vomiting; 0.12 %), nervous system disorders (dizziness, headache, dysgeusia, formication and paraesthesia; 0.11 %), and respiratory, thoracic and mediastinal disorders (cough, productive cough, dyspnoea, oropharyngeal pain and dry throat; 0.06 %). Only six patients (<0.01 %) reported a serious event, including diarrhoea, skin eruption, urticaria, increases in blood creatinine levels, circulatory collapse and renal insufficiency.

Implications for clinical practice

Hypertension is a chronic, often asymptomatic, clinical condition, which requires continuous long-term therapy for effective control. The higher incidence of hypertension in the elderly, plus the fact that it can be more resistant to antihypertensive drug treatment (early-morning BP becomes increasingly uncontrolled, combined with an increased incidence of other cardiovascular risk factors), mean that adequate 24 h BP control becomes increasingly important to prevent acute cardiovascular events. These, together with the knowledge that elderly patients are more likely to have comorbidities and may be taking many other long-term medications in addition to antihypertensive therapy (both of which may have impacts on the pharmacological profile of the drug), mean that an antihypertensive agent with high efficacy, a good tolerability profile and a low propensity for drug interaction is crucial. Additional factors are that OM regimens are simple and straightforward, and are often administered as a once-daily dose, which can be important in maintaining adherence to therapy in elderly patients. Overall, OM fits the bill admirably, providing a convenient, effective and well tolerated option for long-term antihypertensive therapy.

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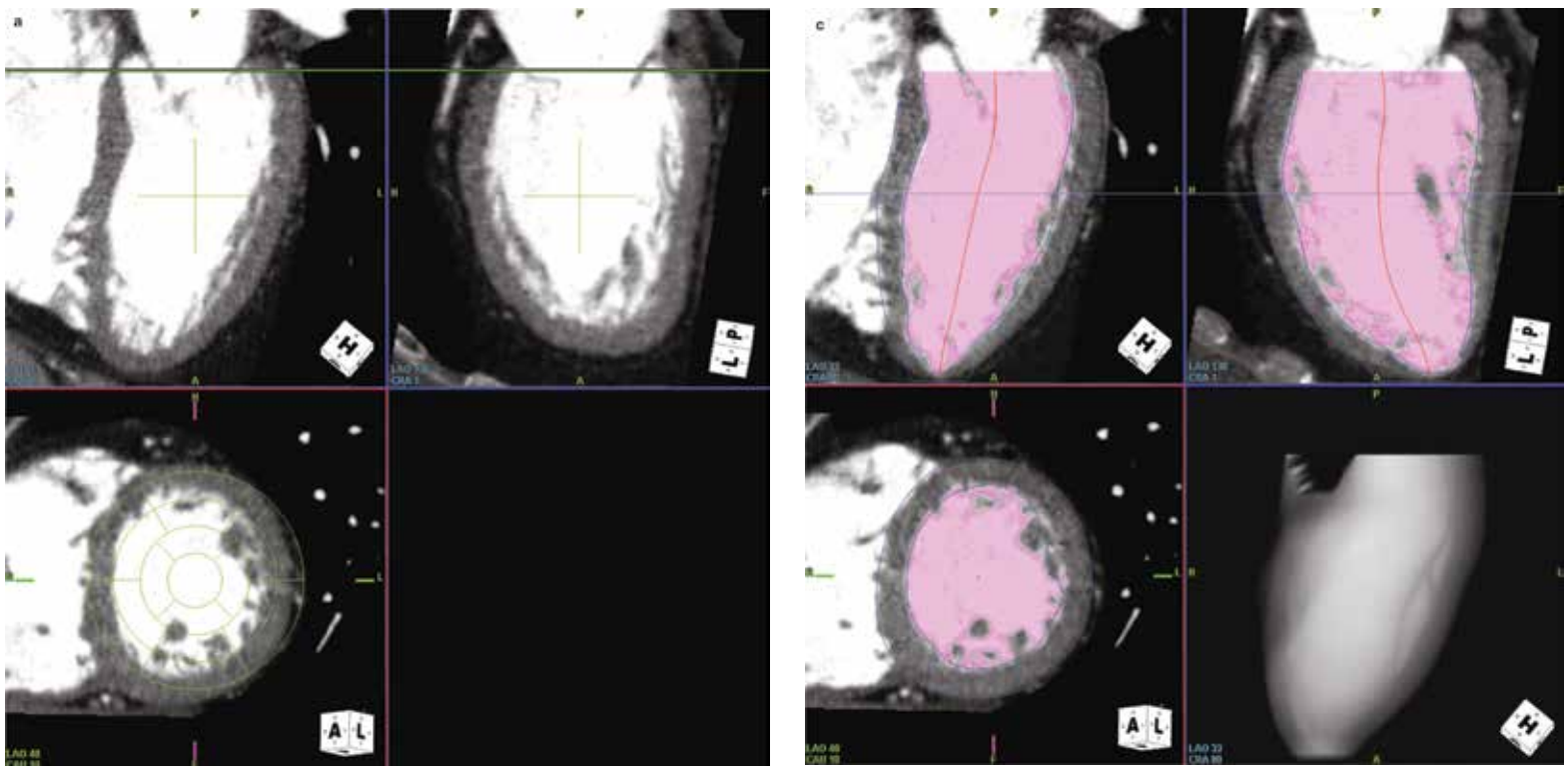
Healthcare.India@springer.com

Source: Massimo Volpe, Giuliano Tocci. Olmesartan in the treatment of hypertension in elderly patients: a review of the primary evidence. Drugs Aging 2013; 30(12):987–998. DOI: 10.1007/ s40266-013-0130-8.

Quantitation of LV (left ventricular) function by cardiac CT



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(**a**) Horizontal long axis, vertical long axis, and short axis views of the left ventricle (LV); the line demonstrates the plane of the mitral valve: when performing quantitative analysis, it is necessary that the LV chamber be isolated. (**b**) Semi-quantitative edge definition of the cardiac endocardial surfaces using thresholding methods; from this information, the LV endocardial (chamber) volumes can be determined. (**c**) Semi-quantitative isolation of the LV myocardial epicardial and septal surfaces using thresholding methods; from this information the LV muscle mass and myocardial wall thicknesses can be determined. (**d**) Lower right of the figure: a color map of the myocardial surface systolic function is defined to provide definition of regional LV function. (**e**) LV chamber volume as a function of time during the cardiac cycle; from these

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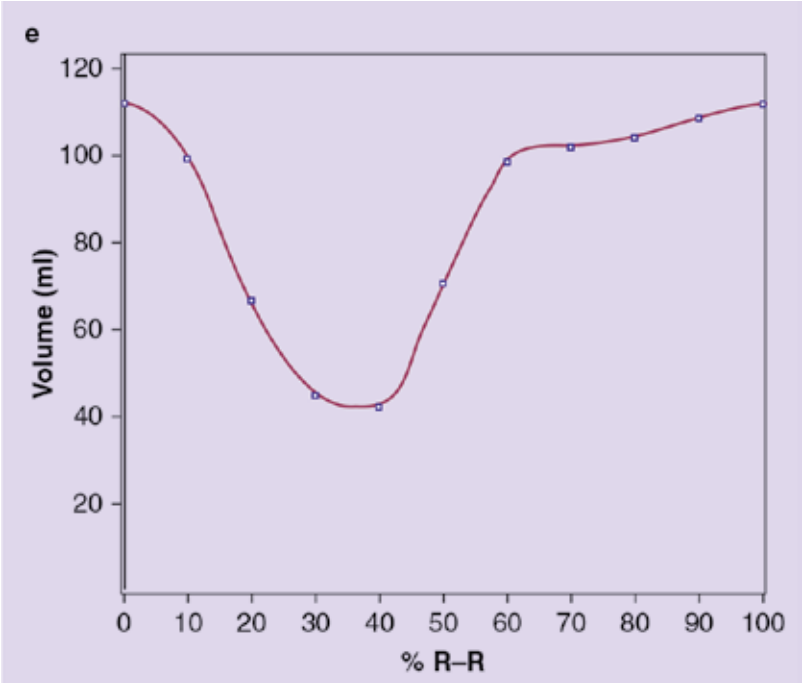

data can be derived information on EF (ejection fraction), *EDV* (end-diastolic volume), *ESV* (end-systolic volume), *SV* (stroke volume), rates of systolic emptying (contractility), as well as rates of early and late diastolic filling (diastolic function).

Source: John A. Rumberger. Assessment of cardiac structure and function by computed tomography angiography. In: Matthew J. Budoff, Jerold S. Shinbane (eds). Cardiac CT Imaging: Diagnosis of Cardiovascular Disease. 3rd ed. Switzerland: Springer International Publishing; 2016, 191-210. DOI 10.1007/978-3-319-28219-0_11. © Springer International Publishing 2016.

Did you know?

There is a link between cardiovascular disease (CVD) and hip fracture

Persons with a diagnosis of heart failure, stroke or coronary artery disease are at increased risk of hip fracture. Heart failure carries the greatest risk with a crude absolute rate of hip fracture ten times greater than persons without a CVD diagnosis [1].

One might logically jump to the conclusion that persons with CVD simply fall more often, explaining the increased incidence of hip fracture. Sennerby, et al. suggest that this is not the case and, instead, that cardiovascular disease and osteoporotic fractures share a common cause. Their study examined identical twins. They found that when Twin A had a cardiovascular disease, there was a greater incidence of hip fracture in Twin B, even when Twin B did not have CVD. They conclude: "Increased risks (of hip fracture) in co-twins without an index diagnosis (CVD) suggest genetic factors in the association between CVD and osteoporotic fractures" [1].

Reference

1. Sennerby U, Melhus H, Gedeborg R, *et al.* Cardiovascular diseases and risk of hip fracture. *JAMA*. 2009;302(15):1666–1673.

Source: Robert B. Taylor. Essential medical facts every clinician should know: to prevent medical errors, pass board examinations and provide informed patient care. 1st ed. New York: Springer. DOI: 10.1007/978-1-4419-7874-5. © Springer Science+Business Media, LLC 2011.

If you see an inverted P wave on an electrocardiogram (ECG), think first of electrode misplacement

Reversed arm leads are the most likely cause of what would be a confusing electrocardiographic finding. Other possibilities are dextrocardia and the very uncommon retrograde atrial depolarization [1, 2].

Reversed arm leads are highly unlikely to occur in an ECG laboratory, but are a very real possibility in a teaching hospital, where inexperienced learners are sent to do an emergency bedside ECG tracing in the middle of the night.

Reference

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Source: Robert B. Taylor. Essential medical facts every clinician should know: to prevent medical errors, pass board examinations and provide informed patient care. 1st ed. New York: Springer. DOI: 10.1007/978-1-4419-7874-5. © Springer Science+Business Media, LLC 2011.

The updated NICE guidelines: cardiac CT as the first-line test for coronary artery disease

Cost-effective care pathways are integral to delivering sustainable healthcare programmes. Due to the overestimation of coronary artery disease using traditional risk tables, non-invasive testing has been utilised to improve risk stratification and initiate appropriate management to reduce the dependence on invasive investigations. In line with recent technological improvements, cardiac CT is a modality that offers a detailed anatomical assessment of coronary artery disease comparable to invasive coronary angiography.

The recent publication of the National Institute for Health and Care Excellences (NICE) Clinical Guideline 95 update assesses the performance and cost utility of different non-invasive imaging strategies in patients presenting with suspected anginal chest pain. The low cost and high sensitivity of cardiac CT makes it the non-invasive test of choice in the evaluation of stable angina. This has now been ratified in national guidelines with NICE recommending cardiac CT as the first-line investigation for all patients presenting with chest pain due to suspected coronary artery disease. Additionally, randomised controlled trials have demonstrated that cardiac CT improves diagnostic certainty when incorporated into chest pain pathways.

NICE recommend cardiac CT as the first-line test for the evaluation of stable coronary artery disease in chest pain pathways.

Source: Alastair J. Moss, Michelle C. Williams, David E. Newby, Edward D. Nicol. The updated NICE guidelines: cardiac CT as the first-line test for coronary artery disease. Curr Cardiovasc Imaging Rep. 2017; 10:15. DOI: 10.1007/s12410-017-9412-6.

Coronary flow reserve in patients with resistant hypertension

Resistant hypertension is associated with increased risk for cardiovascular events. Coronary flow reserve (CFR) is impaired in patients with hypertension and an independent predictor of cardiac mortality. However, there are no published data on CFR in the subset of treatment-resistant hypertension. The aim of this study was to assess CFR in patients with resistant hypertension. Twenty-five consecutive patients with primary resistant hypertension, scheduled for renal denervation, 25 matched patients with controlled hypertension, and 25 healthy controls underwent transthoracic colour Doppler echocardiography at rest and during adenosine infusion. Patients with hypertension were pair-matched with regard to age, sex, ischemic heart disease, diabetes mellitus, smoking status, and body-mass index. Healthy controls were selected according to age and sex. Mean flow velocity was measured in the left coronary anterior descending artery. Baseline mean flow velocities were similar in patients with controlled and resistant hypertension. CFR was significantly lower in patients with resistant hypertension as compared to individuals with non-resistant hypertension (2.7 ± 0.6 vs. 3.1 ± 0.8; $p = 0.03$). Systolic office blood pressure was significantly higher in patients with resistant hypertension (169 ± 20 vs. 144 ± 21 mmHg; $p < 0.01$). Heart rate, ventricular mass, and ejection fraction were similar in the two groups. Healthy controls showed significantly lower baseline velocity, higher CFR, and lower blood pressure as compared to hypertensives. Resistant hypertension was associated with impaired CFR as compared to individuals with non-resistant hypertension indicating impaired cardiac microvascular function which may contribute to the increased risk of adverse outcome in patients with resistant hypertension.

Source: Sebastian Völz, Sara Svedlund, Bert Andersson, Gan Li-Ming, Bengt Rundqvist. Coronary flow reserve in patients with resistant hypertension. Clin Res Cardiol. 2017; 106(2): 151–157. DOI: 10.1007/s00392-016-1043-4.

How to screen for non-adherence to antihypertensive therapy

The quality of assessment of non-adherence to treatment in hypertensive is poor. Within this review, we discuss the different methods used to assess adherence to blood-pressure-lowering medications in hypertension patients. Subjective reports such as physicians' perceptions are inaccurate, and questionnaires completed by patients tend to overreport adherence and show a low diagnostic specificity. Indirect objective methods such as pharmacy database records can be useful, but they are limited by the robustness of the recorded data. Electronic medication monitoring devices are accurate but usually track adherence to only a single medication and can be expensive. Overall, the fundamental issue with indirect objective measures is that they do not fully confirm ingestion of antihypertensive medications. Detection of antihypertensive medications in body fluids using liquid chromatography–tandem mass spectrometry is currently, in our view, the most robust and clinically useful method to assess non-adherence to blood-pressure-lowering treatment. It is particularly helpful in patients presenting with resistant, refractory or uncontrolled hypertension despite the optimal therapy. We recommend using this diagnostic strategy to detect non-adherence alongside a no-blame approach tailoring support to address the perceptions (e.g., beliefs about the illness and treatment) and practicalities (e.g., capability and resources) influencing motivation and ability to adhere.

Source: Pankaj Gupta, Prashanth Patel, Robert Horne, Heather Buchanan, Bryan Williams, Maciej Tomaszewski. How to screen for non-adherence to antihypertensive therapy. Curr. Hypertens. Rep. 2016; 18:89. DOI: 10.1007/s11906-016-0697-7.

Q. 1. Initiating pharmacologic treatment in a 42-year-old woman with DBP of 96 mmHg would likely reduce which one of the following cardiac- and cerebrovascular outcome?

A. Cerebrovascular morbidity and mortality
B. Heart failure
C. Fatal MI
D. Mortality from CHD
E. A and B

The answer is E

According to JNC 8 guideline, there is moderate to high evidence that treating DBP 90 mmHg in adults 30 years of age or older reduces cerebrovascular morbidity and mortality (fatal stroke, nonfatal stroke, or both), and heart failure. However, there is insufficient evidence for fatal MI and mortality from CHD. Thus, E is correct.

Suggested Reading

James PA, Oparil S, Canter BL, *et al.* 2014 Evidence-based guideline for the management of high blood pressure in adults. Report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA* 311 (suppl):79–81, 2014.

Q. 2. You are consulted on a 28-year-old man with IgA nephropathy and proteinuria of 1.2 g/day. His BP is 134/84 mmHg with a heart rate of 70 BPM. His creatinine is 1.0 mg/dL. He has no insurance. Which one of the following medications you recommend to improve his proteinuria?

A. Amlodipine
B. Chlorthalidone
C. Lisinopril
D. Prednisone
E. Atenolol

The answer is C

The JNC 8 and other position statements recommend either an ACE-I or an ARB for patients with CKD and proteinuria as the drug of choice. Lisinopril costs less compared to other ACE-Is. Thus, C is correct. Amlodipine, chlorthalidone, and atenolol can be added, as needed, to control HTN. Prednisone is not indicated in this patient, as ACE-Is or ARBS can improve proteinuria and also BP.

Suggested Reading

James PA, Oparil S, Canter BL, *et al.* 2014 Evidence-based guideline for the management of high blood pressure in adults. Report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA* 311:507–520, 2014.

Q. 3. You see this patient in your office 4 weeks later. Repeat labs show no change other than an increase in serum creatinine from 1.0 to 1.2 mg/dL. His proteinuria decreased from 1.2 g to 0.9 g/day. He is euvolemic. What is your next step in the management of this patient?

A. Discontinue lisinopril and start losartan
B. Discontinue lisinopril and start chlorthalidone
C. Continue lisinopril and follow creatinine and other labs in 2–4 weeks
D. Discontinue lisinopril and start amlodipine
E. Add metoprolol to lisinopril

The answer is C

The patient is responding to lisinopril by improving his proteinuria. An increase in creatinine up to 30 % in response to ACE-Is or ARBs is common, indicating a decrease in glomerular HTN and glomerular filtration. This is a reversible physiologic response and is not harmful. ACE-Is and ARBs also increase serum [K+]. The best thing to do is to continue lisinopril and follow serum chemistry and proteinuria. Thus, C is correct. Other options are not appropriate for this patient at this time.

Suggested Reading

Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: is this a cause for concern? *Arch Intern Med.* 160:685–693, 2000. Hirsch S, Hirsch J, Bhatt U, *et al.* Tolerating increases in the serum creatinine following aggressive treatment of chronic kidney disease, hypertension and proteinuria: pre-renal success. *Am J Nephrol.* 36:430–437, 2012.

Source: A.S. Reddi (ed). Hypertension. Absolute Nephrology Review: An Essential Q & A Study Guide. 1st ed. Switzerland: Springer International Publishing; 2016, 269-311. DOI 10.1007/978-3-319-22948-5_6.

Uncontrolled BP leads to parallel CV & renal disease progression - A Cardio Renal Continuum[1]

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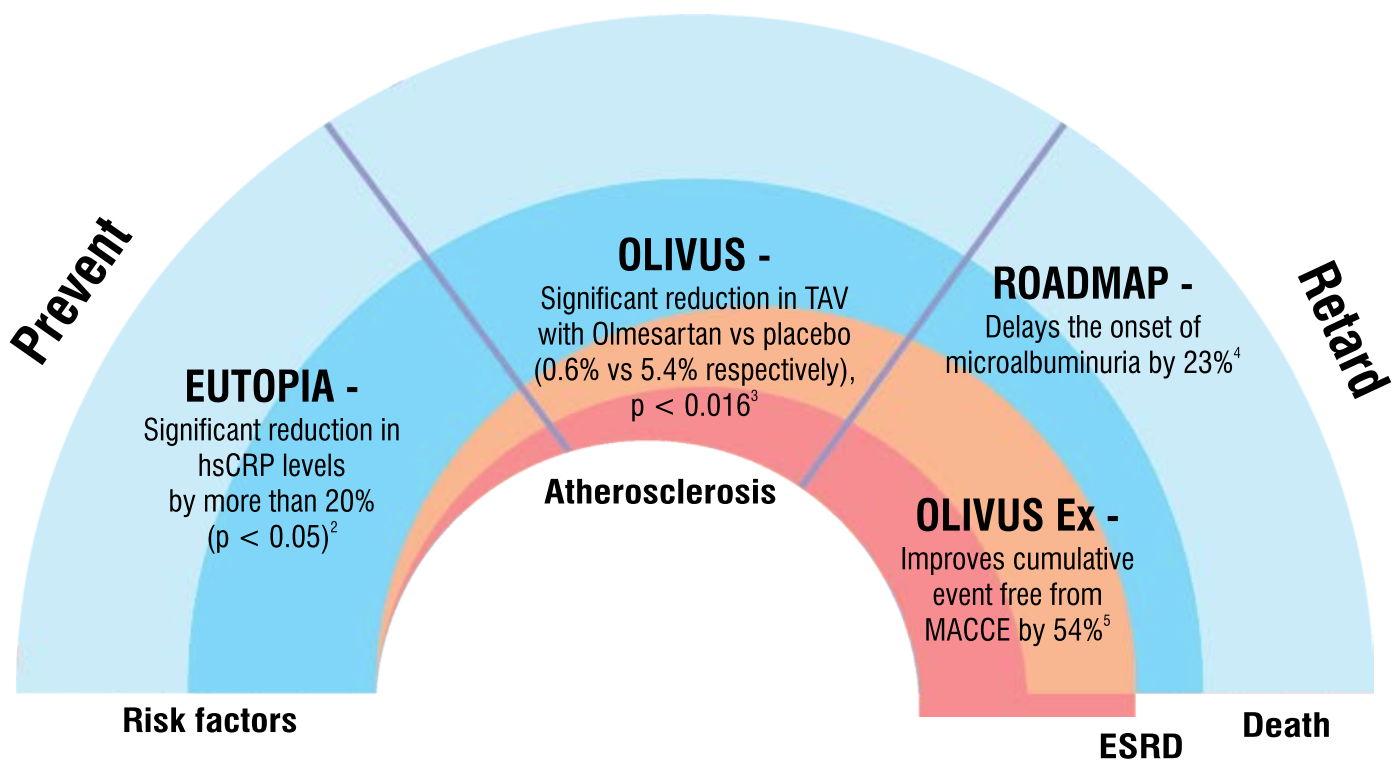

TAV – Total Atheroma Volume, MACCE - Major Adverse Cardio- and Cerebrovascular Events

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4. J Am Heart Assoc. 2014;3:e000810 doi: 10.1161/JAHA.114.000810, mean follow up of 3.2 years 5. Atherosclerosis 220 (2012) 134–138, 4 year clinical outcomes from OLIVUS

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