

Review

Improved Identification and Antihypertension Pharmacotherapy in Cardiorenal Metabolic Syndrome: Focus on Racial/Ethnic Minorities, Olmesartan Medoxomil, and Combination Therapy

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Key Words

Cardiorenal metabolic syndrome • Cardiovascular risk factors • Clinical evidence • Combination therapy • Hypertension • Racial/ethnic minorities

Abstract

Cardiorenal metabolic syndrome (CRS) is a global health care concern in view of aging in certain populations, increased obesity, changing lifestyles, and its close association with type 2 diabetes mellitus and cardiovascular morbidity and mortality. Determining the appropriate criteria for CRS has been somewhat controversial, and efforts to fully describe and define the syndrome are still ongoing. Nonetheless, improving knowledge of the syndrome among health care professionals will help to identify patients who may require pharmacological and therapeutic lifestyle intervention, particularly with regards to addressing high-normal blood pressure and hypertension. This article reviews current clinical guidelines with a focus on the identification, especially in racial/ethnic minorities, treatment, and associated cardiovascular morbidity and mortality of high blood pressure and hypertension in patients with CRS. Efficacy and outcomes studies that provide insight into the selection of an initial antihypertensive regimen in this population will be discussed. Finally, a brief review of the benefits of olmesartan medoxomil and combination therapy and patient factors in the management of hypertension with CRS will be addressed.

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Introduction

Cardiorenal metabolic syndrome (CRS) is a collection of closely related cardiovascular (CV) risk factors that includes elevated blood pressure (BP), dyslipidemia, obesity, and insulin resistance, and differs from the metabolic syndrome (MetS) in that it additionally includes chronic kidney disease (CKD), i.e. microalbuminuria/proteinuria or low glomerular filtration rate (GFR), in the cluster of factors defining MetS [1, 2]. Consequently, much of our current understanding and clinical data pertaining to MetS is also applicable to CRS as the definition of CRS is fundamentally the same as that of MetS, with the addition of a renal component. Moreover, there is a higher prevalence of microalbuminuria in individuals with MetS and, therefore, many of these patients would likely be classified as having CRS. According to 2003–2006 data from the National Health and Nutrition Examination Survey (NHANES), the age-adjusted prevalence of MetS is 35.1% in men and 32.6% in women [3]. The prevalence of CRS/MetS is increasing due to an aging population, population growth, increasing obesity rates, and sedentary lifestyles [4–6]. Along with its increasing prevalence, the association of CRS with type 2 diabetes mellitus (T2DM), CKD [7], and CV disease (CVD) has led CRS to become a prominent public health and clinical concern. Moreover, although there has been a decrease in major risk factors in many countries resulting in reduced CV mortality, body weight and diabetes have continued to increase in contrast to other risk factors such as cholesterol, smoking, and hypertension [8]. The European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam study showed that patients with MetS have a 4.5-fold increased risk of developing T2DM. Furthermore, a meta-analysis by Mottillo et al. [6] demonstrated that patients with MetS had a 2-fold increase in the risk of CVD, CVD mortality, myocardial infarction (MI), and stroke, and a 1.5-fold increase in the risk of all-cause mortality [9]. No race-/ethnicity-specific data were reported in either meta-analysis, and the predictive value of the diagnosis of CRS across various populations needs further elucidation. Coronary heart disease (CHD) and stroke are not only leading causes of death in the United States, but also account for the largest proportion of inequality in life expectancy between whites and blacks, despite the existence of low-cost, highly effective preventive treatment, and the contribution of conventionally defined CRS may be underestimated in African-Americans [10]. Moreover, the prevalence of hypertension, a major modifiable risk factor for CVD and stroke, is much higher for non-Hispanic blacks compared with whites (42 vs. 28.8%) in the United States [11]. Similar to hypertension, the prevalence of CKD is also higher among non-Hispanic blacks (19.9%) than non-Hispanic whites (16.1%) [12].

MetS/CRS Definitions and Diagnosis

While there has been disagreement regarding the appropriate terminology and diagnostic criteria for MetS/CRS, there has been some consensus that MetS/CRS is appropriate to describe a patient having several risk factors for CVD and diabetes [4]. In addition, several organizations have attempted to clarify and define MetS/CRS, including the World Health Organization (WHO), the Third Report of the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III), the International Diabetes Federation (IDF), and the American Heart Association (AHA) (WHO, NCEP ATP III, IDF, and AHA utilize the terminology MetS). Table 1 presents the diagnostic criteria of MetS as it has evolved over time. In clinical practice today, the NCEP ATP III and the IDF definitions of MetS are the most widely used for diagnosis [13].

The first recognized definition of MetS/CRS was developed by the WHO in 1998 to address the clinical need to classify the large number of patients who are at high risk for mac-

Table 1. Diagnostic criteria of MetS as defined by different clinical entities

	WHO 1998	NCEP ATP III 2002	IDF 2006	Consensus definition 2009
	Glucose intolerance, impaired glucose tolerance, or diabetes mellitus and/or insulin resistance PLUS ≥ 2 of the following risk factors:	≥ 3 of the 5 following metabolic risk factors:	Central obesity (by waist circumference – ethnicity-specific values) ^b or BMI $>30 \text{ kg/m}^2$ PLUS ≥ 2 of the following factors:	≥ 3 of the 5 following risk factors:
BP	$\geq 160/90 \text{ mm Hg}$	$\geq 130/85 \text{ mm Hg}$	SBP $\geq 130 \text{ mm Hg}$ or DBP $\geq 85 \text{ mm Hg}$ or current treatment thereof	SBP $\geq 130 \text{ mm Hg}$ and/or DBP $\geq 85 \text{ mm Hg}$ or current treatment thereof
Obesity	Central obesity; waist:hip ratio: >0.90 in men, >0.85 in women, and/or BMI $>30 \text{ kg/m}^2$	Abdominal obesity: $>102 \text{ cm}$ ($>40 \text{ inches}$) in men; $>88 \text{ cm}$ ($>35 \text{ inches}$) in women	See above	Elevated waist circumference (population/country specific) ^c
Triglycerides	$\geq 150 \text{ mg/dl}$ and/or	$\geq 150 \text{ mg/dl}$	$\geq 150 \text{ mg/dl}$ or current treatment thereof	$\geq 150 \text{ mg/dl}$ or current treatment thereof
HDL-C	$<35 \text{ mg/dl}$ in men; $<39 \text{ mg/dl}$ in women	$<40 \text{ mg/dl}$ in men; $<50 \text{ mg/dl}$ in women	$<40 \text{ mg/dl}$ in men; $<50 \text{ mg/dl}$ in women or current treatment thereof	$<40 \text{ mg/dl}$ in men; $<50 \text{ mg/dl}$ in women or current treatment thereof
Fasting glucose	See above	$\geq 100 \text{ mg/dl}$ ^a	$\geq 100 \text{ mg/dl}$ or previously diagnosed T2DM	$\geq 100 \text{ mg/dl}$ or current treatment thereof
Micro-albuminuria	Urinary albumin excretion $\geq 20 \text{ } \mu\text{g/min}$ or albumin:creatinine ratio $\geq 20 \text{ mg/g}$			

^a Represents American Diabetes Association updated criteria (2003); originally impaired fasting glucose was $\geq 110 \text{ mg/dl}$.

^b IDF ethnicity-specific values (male/female) for waist circumference: Europids, Sub-Saharan Africans, Eastern Mediterranean, and Arab populations ($\geq 37/\geq 31.5 \text{ inches}$); Japanese, Chinese, South Asians, and ethnic South and Central Americans ($\geq 35.4/\geq 31.5 \text{ inches}$).

^c Consensus definition recommends 2006 IDF cut-points for non-Europeans and Europeans or a choice of AHA/NHLBI cut-points (male/female) of $>40.2/>34.7 \text{ inches}$ for patients of European descent.

rovascular disease, but may not meet the laboratory definition of diabetes mellitus [14]. The original WHO criteria for CRS were a combination of two markers of insulin resistance plus two or more of the following risk factors: raised arterial pressure ($\geq 160/90 \text{ mm Hg}$), elevated triglycerides, reduced high-density lipoprotein cholesterol (HDL-C), central obesity (measured as waist:hip ratio), or microalbuminuria (which is one of the currently accepted additional criteria for CRS). There are data demonstrating that African-Americans, despite disproportionately high rates of CVD (including MI and stroke), CKD, and diabetes mellitus, have relatively lower, i.e. normal, triglyceride levels and higher HDL-C levels. Although the presence of insulin resistance, T2DM, and CVD tend to be associated with elevated triglycerides, the finding that black individuals with these conditions typically have normal triglyceride levels has led to the use of the term ‘lipid paradox’ or ‘triglyceride paradox’ [15]. Therefore, the inclusion of microalbuminuria may more appropriately identify African-Americans with CRS [16].

In 2002, the NCEP ATP III definition of MetS focused less on insulin resistance as the principal etiological factor and more on obesity and associated CV risk factors. The NCEP

ATP III definition is a positive diagnosis of MetS and requires having three or more of the following five risk factors: abdominal obesity (>40 inches for men; >35 inches for women), elevated triglycerides (≥ 150 mg/dl), decreased HDL-C levels (<40 mg/dl in men; <50 mg/dl in women), elevated BP ($\geq 130/85$ mm Hg), and impaired fasting glucose (≥ 110 mg/dl) [17]. Three major differences between the NCEP ATP III and WHO criteria are the use of waist circumference as a measure of central obesity over waist:hip ratio, the inclusion of a lower BP value compatible with the ‘high-normal’ definition of BP appearing in current practice guidelines at that time [18], and the exclusion of microalbuminuria. Guidelines released in 2005 by the AHA/National Heart, Lung, and Blood Institute (NHLBI) confirmed all of the diagnostic criteria of the NCEP ATP III, with a revised criteria for impaired fasting glucose (≥ 100 mg/dl) [19].

In 2006, the IDF released consensus criteria making central obesity an integral part of the MetS definition. This report included central obesity plus any two of the following four risk factors: raised triglycerides (≥ 150 mg/dl) or treatment for raised triglycerides, decreased HDL-C levels (<40 mg/dl in men; <50 mg/dl in women) or treatment to raise HDL, elevated BP [systolic BP (SBP) ≥ 130 mm Hg or diastolic BP (DBP) ≥ 85 mm Hg] or currently on antihypertensives, or raised fasting plasma glucose (≥ 100 mg/dl) or previously diagnosed T2DM [20]. Central obesity was defined according to ethnicity-specific values or if the patient had a body mass index (BMI) >30 kg/m². In addition to redefining clinical criteria associated with abdominal obesity, the IDF integrated the lower blood glucose value as indicative of impaired fasting glucose at 100 mg/dl from 110 mg/dl.

Furthermore, a joint consensus statement from the IDF, NHLBI, AHA, World Heart Federation, International Atherosclerosis Society, and the International Association for the Study of Obesity was released in 2009 to resolve differences in the MetS definition [4]. Central to the discussion was whether central obesity should be an obligatory component of the MetS definition and whether waist circumference values should reflect differences in ethnicity, country, and sex. The consensus group concluded that waist circumference should not be an obligatory part of the MetS diagnosis. Instead, it would become one of five measures, of which three were needed for a positive diagnosis. Citing a need for continued research regarding waist circumference thresholds, the group in the interim suggested waist circumference values based on national, regional, or ethnic differences for men and women.

Race/Ethnicity and Controversy in MetS/CRS Diagnosis

Using the NCEP ATP III guidelines and 2003–2006 data from NHANES, the National Center for Health Statistics examined the prevalence of MetS in the United States among persons aged ≥ 20 years [5]. Of the 3,423 patients surveyed, the crude, age-adjusted prevalence of MetS was 34%. Among men, 37% of non-Hispanic whites met the NCEP ATP III criteria of MetS compared with 33% of Mexican-Americans and 25% of non-Hispanic blacks. As previously mentioned, the low rates in black men are paradoxical considering the high rates of hypertension [3] and diabetes [21], two of the major diagnostic criteria of MetS/CRS, and high rates of overall CVD [10]. Considering the disproportionate rates of CVD and CKD in black men and the greater likelihood of death from CHD and stroke [10], the finding that non-Hispanic black men were half as likely as non-Hispanic white men to satisfy the MetS/CRS criteria is a conundrum.

Mexican-American women had an estimated prevalence of 40.6%, compared with 38.8% in non-Hispanic black and 31.5% in non-Hispanic white women [5]. Similar to black men, the relatively lower rates of MetS/CRS in black women contradicts the higher rates of hypertension and obesity versus all major race/ethnic categories [3], the greater likelihood of death due

to CHD versus all races [10], and higher or, at best, similar diabetes rates to Mexican-American women [5]. While non-Hispanic black and Mexican-American women were 1.5 times more likely to meet the MetS criteria than non-Hispanic white women, black women have much higher overall CVD, morbidity, and mortality than either non-Hispanic whites or Mexican-American women [5, 10]. These overall race- and sex-based patterns of MetS were similar to those reported in 2002 by Ford et al. [22] using NHANES data from 1988–1994.

Considering the above data and other findings, despite wide clinical use of the NCEP ATP III criteria, the optimal means for identification of MetS/CRS in African-Americans remain unclear. Compared with studies using other MetS/CRS definitions, the prevalence in ATP III-based studies tends to be lower because central obesity is not an obligatory component of the definition [23–25]. Another issue is the cut-off values for triglyceride and HDL-C levels. As previously noted, African-Americans tend to have lower triglycerides and higher HDL-C levels than non-Hispanic whites [26–28]. These considerations call into question whether race-/ethnicity-based criteria should be considered for all parameters of the MetS/CRS diagnosis, not just for waist circumference. Considering that black men and, to some extent, black women are underdiagnosed using the most popular current MetS definitions, studies are needed to explore population-based differences in biometrics in order to enhance the sensitivity of the MetS/CRS definition, and clinicians should recognize that the current MetS/CRS definition is not ‘one size fits all’.

Management of High BP and Hypertension in MetS

CVD risk increases in a linear fashion before conventional hypertensive BP levels are reached. Current practice guidelines arise out of the detailed assessment of available clinical evidence and define hypertension as an SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg [29, 30], which is well above optimal or normal levels. For most patients, a treatment goal BP of $<140/90$ mm Hg is recommended, while for patients with renal disease or diabetes mellitus, a more stringent goal of $<130/80$ mm Hg has been recommended [29, 30]. It should be noted that prospective clinical trial data do not currently support starting antihypertensive drug therapy in patients with diabetes and high-normal BP, and therefore it may be beneficial to initiate such therapy only if subclinical organ damage is present [8]. In fact, the recent 2012 joint European Society of Hypertension/European Society of Cardiology (ESH/ESC) guidelines on CVD prevention recommend that the BP target in patients with diabetes should be $<140/80$ mm Hg.

However, there are CV risks associated with BP levels below this somewhat arbitrary hypertension threshold, described in different guidelines as prehypertension (SBP of 120–139 mm Hg or DBP of 80–89 mm Hg) [29] or high-normal BP (SBP of 130–139 mm Hg or DBP of 85–89 mm Hg) [30]. Beginning with a BP of 115/75 mm Hg, every 20-mm Hg increase in SBP and every 10-mm Hg increase in DBP doubles the risk of death due to stroke, angina, MI, and heart failure [31]. Therefore, the recognition of increased CVD risk before the arbitrary BP level defined as hypertension is important in patients with MetS/CRS, who are likely to have elevated BP. In patients with MetS aged 39–64 years, rates of high BP (defined as SBP ≥ 130 mm Hg or DBP ≥ 85 mm Hg) range from 39 to 50% in men and from 29 to 40% in women [32], and, not unexpectedly, rates of high BP are 70–80% in men and women aged ≥ 65 years [32]. Consequently, it may be beneficial to initiate BP-lowering therapy before apparent organ damage, or while it is still reversible [8].

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) and the 2007 ESH/ESC hypertension treatment guidelines advised managing patients with MetS who have prehypertension or

high-normal BP by encouraging lifestyle modifications [29, 30]. Beyond lifestyle modifications, the JNC 7 treatment guidelines do not specifically address pharmacological management of BP in the patient with MetS until BP exceeds the threshold of 140/90 mm Hg, unless comorbid T2DM or renal disease are present. In patients with MetS, the 2007 ESH/ESC guidelines advise clinicians to *consider* pharmacotherapy along with lifestyle modifications in high-normal BP; however, they also note these recommendations are not firm because of the lack of interventional trials in this population [30]. As to choosing the most beneficial antihypertensive agent for MetS/CRS, the 2007 ESH/ESC guidelines recommend an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB) not only because they may help delay the progression to hypertension and T2DM, but also due to their superior protective effect against initiation or progression of nephropathy/renal damage [8, 30, 33, 34]. However, the upcoming JNC 8 hypertension guidelines may re-evaluate the current BP goal of <130/80 mm Hg for patients with hypertension, T2DM, and CKD, considering limited clinical evidence from major outcomes trials [35, 36].

Considering the high rates of obesity, dysglycemia, and CKD, achieving BP control can be difficult in patients with MetS/CRS, who are also more likely to have treatment-resistant hypertension. According to NHANES data from 2007–2008, only 50% of all patients with diagnosed hypertension achieve BP control [37]. Clinicians need to be aware that, for most patients, BP control rates range from 27 to 37% with antihypertensive monotherapy, versus as high as from 53 to 75% with combination therapy [38–40].

When monotherapy fails to achieve the BP goal in patients with hypertension and MetS, the 2007 ESH/ESC guidelines recommend adding a calcium channel blocker (CCB) to an ACEI or ARB, or using a thiazide diuretic as second- or third-line therapy [30]. Data have shown that three agents may be required to control BP in 15–20% of patients with hypertension, and using a renin-angiotensin system (RAS) blocker, CCB, and diuretic appears to be a rational combination [41]. Combining agents from different antihypertensive drug classes results in BP lowering approximately five times greater versus doubling the monotherapy dose [41]. Furthermore, fixed-dose combinations (FDCs) may increase compliance by simplifying treatment regimens. Compared with a β -blocker/thiazide diuretic combination, a CCB/ACEI combination prevented more total CV events and procedures (1,362 vs. 1,602; $p < 0.0001$) and new-onset diabetes cases (567 vs. 799; $p < 0.0001$) in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) [42]. However, these were secondary endpoints, and no statistically significant difference was detected in the primary endpoint, the composite of nonfatal MI (including silent MI) and fatal CHD (429 vs. 474 cases; $p = 0.1052$). In recognition of the difficulty translating European data to a more heterogeneous US population, it is noteworthy that only approximately 5% of the study population in ASCOT-BPLA was black [43].

The case for utilization of a RAS blocker plus CCB combination therapy was supported in the Avoiding Cardiovascular Events Through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial, wherein a benazepril (BEN) plus amlodipine (AML) treatment regimen prevented more primary outcome events (death from CV causes and CV events) than BEN plus hydrochlorothiazide (HCTZ; $p < 0.001$) [40]. A recent subgroup analysis of ACCOMPLISH evaluating renal outcomes in the black cohort of the study population demonstrated that there was no difference in mean estimated GFR loss in the black cohort between the treatment regimens; however, BEN/AML combination therapy was more effective than BEN/HCTZ in stabilizing estimated GFR/reducing kidney disease progression in non-blacks [44]. There was no difference between the black and non-black cohorts for the composite kidney disease endpoint (i.e. doubling in serum creatinine, end-stage renal disease, or death), although black patients were significantly more likely to have a >50% increase in serum creatinine.

In The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [45], there was no significant difference in the primary endpoint of fatal CHD or nonfatal MI between chlorthalidone and lisinopril or AML [46]. Furthermore, in a subgroup analysis of patients with MetS or diabetes, there were no significant differences in the relative risks of CHD, all-cause mortality, stroke, or end-stage renal disease in patients treated with chlorthalidone compared with either lisinopril or AML [47]. However, the risk of heart failure and combined CVD was significantly greater in patients with MetS treated with lisinopril versus chlorthalidone [47]. Recent data from the ALLHAT Diabetes Extension Study showed that in those study patients who developed incident diabetes mellitus versus non-diabetic patients, the lowest hazard ratios for CVD mortality, total mortality, non-CV mortality, CHD, and stroke were observed in the chlorthalidone group [48]. Incident diabetes mellitus did not have a significant adverse effect on the risk for any outcome in the chlorthalidone group. For a patient who is naïve to antihypertensive therapy, treatment with a thiazide-type diuretic is considered a good first choice on the basis of these endpoints alone. However, as previously noted, most patients require combination therapy, and the ALLHAT study design did not assess the benefits of structured combination therapy, such as a RAS blocker paired with a thiazide-type diuretic or CCB, as commonly prescribed today. Of the total ALLHAT study population, approximately 32% of randomized patients were black and 16% were Hispanic [46].

In the Losartan Intervention for Endpoint Reduction (LIFE) study [39], 508 patients in the losartan group and 588 patients in the atenolol group reached the primary composite endpoint (CV death, MI, and stroke) at study end. This was a statistically significant finding before and after adjustment for the Framingham Risk Score ($p = 0.009$ and $p = 0.021$, respectively) [39]. In addition, the losartan group experienced significantly fewer incidences of stroke than the atenolol group (232 vs. 309; $p = 0.001$ and $p = 0.0006$ before and after adjustment, respectively) [39]. A significantly lower incidence of new-onset diabetes was seen in losartan patients not having diabetes at baseline (6 vs. 8%; $p = 0.001$ for both adjusted and unadjusted analyses) [39]. Unfortunately, the black and Hispanic cohorts were too small (6 and 1%, respectively) to confirm any CVD or stroke benefit with an ARB-based regimen [39, 49]. Importantly, a recent substudy of LIFE evaluating racial differences in sudden cardiac death showed that the 5-year sudden cardiac death incidence was significantly higher in black versus non-black patients (3.9 vs. 1.9%; $p = 0.007$). Even after multivariate Cox analyses, black race was associated with a 98% increased risk of sudden cardiac death ($p = 0.020$) [50].

In the BP arm of the Action to Control Cardiovascular Risk in Diabetes (ACCORD BP) trial [35], patients were randomized to intensive or standard BP control [51]. For the primary outcome (composite of nonfatal MI, nonfatal stroke, and CV death), there were 208 events in the intensive versus 237 in the standard therapy group ($p = 0.20$) [35]. For the secondary endpoints of any stroke and nonfatal stroke, there were statistically significantly fewer events for both in the intensive versus standard control groups ($p = 0.01$ and $p = 0.03$, respectively) [35]. This finding could indicate some benefit attributable to the lower mean SBP achieved in the intensive versus standard therapy group (119 vs. 133 mm Hg, respectively). Therefore, despite the nonsignificant findings of the primary endpoint, achieving a lower BP in patients with T2DM at higher risk for stroke may be advisable. It remains unclear whether this finding will prompt a revision of hypertension or MetS/CRS guidelines, especially considering the statistically insignificant higher incidence of deaths from any cause observed in the intensive treatment group (150 vs. 144; $p = 0.55$) [35]. The American Diabetes Association 2012 practice recommendation notes a BP goal of <130/80 mm Hg for persons with diabetes, which may be lower or higher depending on individual patient characteristics [52]. Although no specific race/ethnicity data were reported, approximately 24% of the study population in ACCORD was black and 7% Hispanic [35].

Recent Olmesartan Medoxomil Efficacy Studies Supporting a RAS Inhibitor-Based Treatment Strategy

Although CVD morbidity/mortality studies are essential to determine guidelines and evidence-based antihypertensive therapy, recent olmesartan medoxomil (OM) efficacy studies support the utilization of RAS blockers, alone or in combination, to achieve the BP goal in patients at increased risk. An ambulatory BP (ABP) monitoring study assessed the efficacy of an AML/OM \pm HCTZ combination therapy in patients with hypertension and T2DM [53]. At baseline, the mean 24-hour ABP was 144.4/81.6 mm Hg. After 12 weeks of active treatment, the mean ABP was significantly reduced by $-19.9/-11.2$ mm Hg ($p < 0.0001$ vs. baseline), with 72% of patients titrated to triple therapy (AML/OM + HCTZ) [53]. Approximately 70% of the patients achieved a 24-hour ABP target of $<130/80$ mm Hg. The seated cuff (Se) BP goal of $<130/80$ mm Hg for patients with T2DM was achieved by 62% of the patients after 18 weeks of treatment [53]. Blacks and Hispanics comprised 17 and 26% of the study population, respectively [53], and 81% of the patients had MetS [54].

Another study investigated BP goal achievement in patients with hypertension (46.2% had MetS) inadequately controlled on antihypertensive monotherapy who were switched to an AML/OM \pm HCTZ combination therapy titration regimen [55]. After 12 weeks of treatment, 75.8% of the patients achieved the SeSBP goal of <140 mm Hg (or <130 mm Hg for patients with diabetes) [55]. The BP goal of $<140/90$ mm Hg ($<130/80$ mm Hg if diabetes) was achieved by 71.3 and 84.8% of the patients by weeks 12 and 20, respectively, and 90.3% achieved the cumulative BP threshold of $<140/90$ mm Hg by week 20 [55]. The study population consisted of 23.4% black patients and 10.5% Hispanic patients [55]. Preliminary data from a 2010 abstract demonstrated that, at any time point by week 20, a cumulative SeBP goal of $<140/90$ mm Hg was achieved by 86.6 and 88.0% of black and Hispanic patients, respectively [56]. Other RAS-blocking agents in combination with AML/HCTZ are also available and have demonstrated efficacy in achieving BP goals (see online suppl. table; www.karger.com/doi/10.1159/000342968).

Potential Benefits of FDC Therapy

Patients with MetS/CRS are often being treated concomitantly for other metabolic abnormalities such as dyslipidemia, glucose intolerance, or insulin resistance. Managing hypertension in these patients can increase pill burden as multiple medications may be needed [38]. When appropriate and possible, clinicians should strive to simplify treatment regimens through the use of FDC (single-pill) therapy. Once-daily FDC formulations decrease the daily pill burden and may improve adherence. In a randomized trial in Canada, a simplified treatment regimen utilizing FDC therapy and a clearly defined algorithm for dose escalation was compared with conventional guideline-based care for achieving the BP goal. At 6 months, 64.7% of the patients in the FDC therapy simplified treatment arm achieved the BP goal versus 52.7% in the conventional treatment group ($p = 0.026$) [57].

In a meta-analysis of nine studies reporting adherence data, FDC therapy reduced medication nonadherence by 26% ($p < 0.0001$) versus non-FDC regimens [58]. A subgroup analysis of the four antihypertensive therapy studies showed that FDC therapy decreased medication nonadherence by 24% ($p < 0.0001$) [58]. FDCs combining the benefits of RAS blockers with HCTZ are available, as are combinations with CCBs, and should be considered when appropriate for the management of hypertension.

FDCs may not be of benefit to all patients. FDC antihypertensives can be more expensive than the generic component medications. Not excluding the uninsured, the coverage pro-

vided by insurance plans, Medicare, and Medicaid may make FDC therapy too expensive for lower-income patients or for patients for whom cost concerns may outweigh the benefits of decreased pill burden or improved adherence. Although generic substitution programs offered by major pharmacy chains provide lower-cost access to antihypertensive agents, unfortunately, the generic formularies usually offer a limited range of agents, including fewer FDCs [43]. Alternatively, pharmaceutical industry patient-in-need programs can provide some branded antihypertensive agents at zero cost to the patient. Another important consideration with FDCs is that they may limit the flexibility to adjust the dosage of one component depending on a variety of clinical scenarios. Finally, it may not always be apparent which component of an FDC is responsible for an adverse event or intolerance.

Conclusions

A need exists to increase scientific knowledge with regards to MetS/CRS and diagnostic criteria. CKD has increased to epidemic proportions across the industrialized nations and is even more prevalent in socioeconomically deprived individuals and minorities. Moreover, patients with CRS are identified to be at greater risk for developing CKD. Consequently, it is imperative that patients with MetS, especially those populations at increased risk for CKD, be evaluated for microalbuminuria and/or reduced renal function in order to reduce the number of patients developing CKD and end-stage renal disease. Studies focusing specifically on racial/ethnic minorities will help to broaden the available data for consideration when constructing future practice guidelines and ensure that diagnostic criteria do not leave certain ethnic or racial populations underdiagnosed. MetS/CRS is quickly becoming a global health epidemic because of its increased prevalence and association with CVD, diabetes mellitus, and CKD, and associated health care costs are expected to rise dramatically in developed countries. Considering the association of hypertension with increased CV mortality, effective lifestyle modifications and antihypertensive therapy are important. Given that patients with MetS/CRS have multiple comorbidities and, therefore, receive numerous risk-reducing medications, appropriate antihypertensive fixed-dose double or triple combination therapy should be considered whenever appropriate. By recognizing and effectively treating risk factors associated with MetS/CRS, clinicians can potentially improve patient outcomes and help to reduce the burden on health care resources imposed by MetS/CRS and its complications.

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