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Hypertension and Health Behaviors in Females across the Lifespan

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This symposium presentation focused on hypertension and health behaviors in girls and women and provided contrasts with boys and men. I am honored to have copresented with my esteemed colleague, Dr. Suzanne Oparil from the University of Alabama at Birmingham. A long-time supporter of SSCI and the 1st woman to receive the SSCI Founder's Medal Award; Suzanne has been a role model for me and many others engaged in cardiovascular research.

The goals of this symposium presentation were to provide an overview of cardiovascular disease in women versus men, review hypertension as an ongoing public health and clinical challenge in girls and women, highlight hypertension as a key risk factor for cardiovascular disease (CVD) in females and reflect on lifestyle and medication adherence behaviors to improve hypertension control and reduce CVD risk across the lifespan.

Cardiovascular Disease Overview

Heart disease is still the leading cause of death among women and men; and according to the U.S. Census Bureau and the National Vitals Statistics System, death rates for women and men are most prevalent in the southeastern US. From 1980 to 2011, there has been a substantial decline in CVD mortality rates in women and men; however, a narrow yet persistent gap remains with CVD death rates higher in women compared to men.[1] The improvements in CVD death rates in women are attributed in part to improved practice of CVD prevention in women due to results reported from major randomized trials such as the Women's Health Initiative and development and dissemination of women-specific clinical recommendations for prevention of CVD.[2] More recent publications have reported a nearly doubling of the rate of public awareness of CVD as the leading cause of death among US women (from 30% in 1997 to 56% in 2012) and 65% of women reporting that the first thing they would do if they thought they were having a heart attack is call 9-1-1.[3] Currently, a little over one third of adults have some form of CVD with the prevalence of CVD in

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women being lower compared to men (34% versus 36.7%).[4] Despite advances in CVD prevention and mortality risk reduction in women and men, persistent challenges remain: coronary heart disease rates in middle aged women are increasing and parallel the increase rates of obesity; racial disparities exist with higher CVD rates in black versus white females; higher rates of stroke in women compared to men; and poor health system performance with respect to achieving blood pressure (BP) control.[3;5] The ongoing challenges signal an opportunity to increase prevention messages to younger women, an age group with potentially modifiable risk factors related to pregnancy (e.g., gestational diabetes and pre-eclampsia) and with opportunity to reap substantial benefit from healthy lifestyles and other preventive behaviors. The challenge of CVD in women is going global,[2;3;6] and efforts to improve health behaviors and risk reduction are urgently needed.

Hypertension in Children and Adults

Hypertension is a key modifiable risk factor for both CVD and end stage renal disease.[7] It is the leading outpatient diagnosis for women and men, and the prevalence of hypertension is significantly increasing in girls[8;9]. Although there has been progress in the prevention, detection, awareness and treatment of hypertension, it persists as a major public health challenge affecting over 80 million adults in the US and over a billion people worldwide[1;10]. Although initially considered a disease of adults, hypertension is increasing in children and adolescents.

Although the overall prevalence rate of 5% for essential hypertension in girls and boys is low, high BP is a growing problem in youths and is often overlooked by physicians and other healthcare providers.[11] Normal BP values in children and adolescents are based on the individual's age, sex, and height. Pre-hypertension is defined as a BP in at least the 90th percentile, but less than the 95th percentile, for age, sex, and height, or systolic BP (SBP) / diastolic BP (DBP) measurement of 120 mm Hg/80 mm Hg or greater. Hypertension is defined as BP greater than or equal to the 95th percentile for age, sex, and height (using standardized tables) on at least 3 occasions.[12] Primary hypertension correlates strongly with overweight and obesity in this age group.[8;9] Rosner et al reported that the prevalence of elevated BP (SBP or DBP ≥90th percentile or SBP/DBP ≥120/80 mm Hg) in children has significantly increased from 1988 to 2008 with part of the increase attributable to changes in obesity and sodium intake. Specifically, the prevalence of elevated BP increased from NHANES III to NHANES 1999–2008 in boys: 15.8% to 19.2%, P=0.057 and in girls: 8.2% to 12.6%, P=0.007. After adjustment for age, sex, race/ethnicity, body mass index, waist circumference and sodium intake, the odds ratio (OR) for elevated BP in youths using NHANES 1999 to 2008 versus NHANES III was 1.27 (95% confidence interval [CI], 0.98–1.64), P=0.069. Girls had a 43% higher OR for elevated BP comparing NHANES 1999 to 2008 with NHANES III.[9]

In adults, the prevalence rate of hypertension increases with age in both men and women. The residual lifetime risk for hypertension for middle-aged and elderly individuals is 90%, indicating a major public health burden.[13] In women, there is an increase in prevalence of hypertension after menopause[14]. Over time, there have been improvements in awareness, treatment and control of hypertension in both women and men; however, women compared

to men reported higher rates in all three categories.[15] Despite relatively high rates of awareness (74%) and treatment (72%) for hypertension, 53% of adults still have uncontrolled hypertension and are not reaping the health benefits of disease control.[15] Recent data trends suggest that treatment rates continue to increase, whereas the rates for awareness and control appear to have plateaued. Poor health-related behaviors such as obesity, sodium intake and poor medication adherence may negatively impact hypertension control. Uncontrolled hypertension is linked to CVD risk in females and males.[1] The damage to target organs such as the heart and kidneys is a function of hypertension and associated risk factors including diabetes, hyperlipidemia, and tobacco abuse.

Health Behaviors and other Cardiovascular Risk Factors

In looking at the traditional risk factors for CVD in adults—hypertension, hyperlipidemia, diabetes, smoking, obesity and physical inactivity-there are differences in women versus men.[1;16] Hypertension is less prevalent in younger women versus younger men. After age 60, the prevalence is higher among women versus men. Hormones are likely contributing factors (androgen and female sex hormones). The prevalence of elevated lipids appear to differ by sex. Women versus men with diabetes have a higher mortality rates. Although smoking rates are higher among men compared to women, the declines in smoking rates were slower in women than men. Evidence to date indicates that the risk of coronary heart disease is greater for women who smoke than for men who smoke. Obesity and physical inactivity differ by sex. Women are more likely than men to be physically inactive. Both men and women are less likely to be active when weather conditions are unfavorable; but women are less likely to increase activity when weather conditions become more favorable. The most commonly reported barrier to activity in women is lack of time due to family obligations. Further contributing to the complexity of disease management are the racial gaps in CVD risk factors.[1] Compared to men and white women, black and Mexican American women have higher prevalence of obesity and diabetes; black women have higher prevalence of hypertension. Smoking prevalence is higher in men and white women compared to women in other racial groups. In addition to traditional risk factors, there is mounting evidence that other exposures in childhood may adversely affect CVD risk in adulthood. In a study of over 11,000 adolescents participating in the National Longitudinal Study of Adolescent Health, the association between self-report recall of maltreatment (e.g, child neglect, physical and sexual violence) prior to 6th grade was associated with hypertension in young adulthood. Specifically, young women who experienced sexual abuse in early childhood had a higher prevalence of hypertension (adjusted prevalence ratio 1.43; 95% CI, 1.00–2.05); no association in men.[17] The prevalence of traditional risk factors in children and adolescents tend to differ depending on sex (female, male) and the age group (ages 2–5, ages 6–11, and aged 12–19). Some risk factors (e.g., obesity) appear to be influenced by socio-demographic determinants as well.[1]

Management of Essential Hypertension

Appropriate management of hypertension can improve BP control and reduce CVD risk. The cornerstones of hypertension management are lifestyle modifications (e.g., diet, exercise, smoking cessation) and medications. Adherence to lifestyle modifications is

challenging and may take time to achieve disease control. If efforts to improve lifestyle to achieve disease control are not successful, then addition of effective medications to the treatment regimen is warranted.

Essential hypertension occurs in children although secondary hypertension is more common in children and adolescents than it is in adults (a discussion of secondary hypertension is beyond the scope of this presentation). In evaluating youths identified as having essential hypertension, it is important to screen for other CVD risk factors including diabetes and hyperlipidemia and evaluate for target organ damage (e.g., retinal examination).[11;12] (note that the 2013 U.S. Preventive Services Task Force rendered that there is inconclusive evidence to assess benefits and harms of screening for primary hypertension in asymptomatic children and adolescents to prevent CVD disease[18]). Lifestyle modifications including proper diet, exercise, reducing smoking and alcohol intake, weight reduction in overweight and obese individuals and stress reduction are the first lines of management. Antihypertensive medications are indicated if hypertension is symptomatic, persistent, secondary hypertension is determined, target organ damage exists, or diabetes is a comorbid condition. Thiazide diuretics, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta blockers and calcium channel blockers have been determined to be safe, effective and well-tolerated.[11;12] Attention must be given to medication adherence in children and adolescents treated for hypertension.

The evidence-based guideline for the management of high BP in adults and the report from the panel members appointed to the Eighth Joint National Committee (JNC 8) was published in 2014. The JNC 8 focused on data from randomized controlled trials as providing the gold standard to assess benefits and harms of treatments;[19] there a number of changes from the JNC 7 recommendations.[20] The current guideline provides evidence-based recommendations for the management of high BP and should meet the clinical needs of most women and men; however, the authors note these recommendations are not a substitute for clinical judgment, and decisions about care must carefully consider and incorporate the clinical characteristics and circumstances of each individual patient. Although discussion about the impact of the JNC8 on hypertension management and the details of the guidelines is beyond the scope of this presentation, it is important to note the changes and, in particular, the inclusion of reinforcement of adherence to medication and lifestyle changes throughout the guideline recommendations.

Adherence to Medications

Effective medical therapies (including multiple classes, once daily dosing and combination drugs) and evidence-based guidelines exist to lower BP and reduce the risk for CVD; however, approximately 50% of patients do not take chronic medications as prescribed,[21;22] and only 68.9% of U.S. adults treated for hypertension have controlled BP.[14]. Poor adherence to antihypertensive therapy has been associated with worse BP control, increased hospitalization rates, higher health care costs and lower survival.[22–28] Low adherence to antihypertensive medication remains a public health and clinical challenge.

Because hypertension management may require use of multiple drugs to achieve BP control and will require continuous adherence (i.e. persistence) to pharmacologic treatment over time to achieve and maintain BP control and reduce the risk for CVD and related deaths,[29–31] there is a recurring cost and inconvenience of long-term therapy. The fact that hypertension is typically an asymptomatic disease—with the treatment seemingly worse than the disease itself due to side effects-further complicates management of this disease.[22;32;33] Side effects of medications such as fatigue, sexual dysfunction, and frequent urination are some of the barriers to long-term adherence.

Former U.S. Surgeon General C. Everett Koop noted “drugs don’t work in patients who don’t take them” and the National Council on Patient Information and Education described low adherence as “America’s other drug problem”. The World Health Organization has identified poor adherence as a worldwide problem.[34] With increasing emphasis on health outcomes and patient safety from insurers, accountable care organizations and consumers, the focus on patient adherence to prescribed therapies is here to stay. It has been suggested that improving the effectiveness of adherence interventions may have a far greater impact on population health than any improvement in specific medical therapies.[21;34–36] Health systems must evolve to meet the new challenges and improve medication adherence.[34] Understanding of the multifactorial and dynamic nature of adherence behaviors, the need to support and not blame patients, identification of patient-tailored interventions, engagement of family and community members to address the issue, and multidisciplinary approach with trained health professionals will be key to success.[34]

Children with essential hypertension have difficulty adhering to their treatment regimen; differences in girls and boys have not been well studied. Adding to the complexity, in children and adolescents, adherence to medications and other therapies is not only a function of the child but also of the parent and/or guardian. Although few data are available regarding adherence to antihypertensive medications, one study including 21 adolescents with essential hypertension reported that African American adolescents had lower medication adherence assessed by pharmacy fill medication possession ratio (MPR) than non-African American adolescents; adherence was associated with BP with low adherers having worse BP control.[37] Additional data on adherence to medical follow-up visits in pediatric patients with chronic disease has been examined and may provide insight related to medication adherence. Factors associated with nonadherence to medical follow-up visits include lower socioeconomic status,[38;39] transportation issues, being the child of a single parent,[40] perception of the seriousness of the child’s illness,[41] and ethnicity and insurance type.[42] Adherence in the pediatric population is likely negatively impacted by the asymptomatic and lifelong nature of hypertension, side effects and inconvenience of treatment, and health illiteracy. Developmental and family characteristics represent additional risk factors of poor adherence in pediatric patients[43]. More recently, the influence of personality dimension such as conscientiousness and agreeableness and the child’s perception of the their illness have been found to be associated with adherence behaviors.[44] In considering interventions to improve adherence, it is important to direct educational efforts to increase adherence to both the parent/guardian and the child.

In adult populations, there is increasing evidence that adherence to medications may be worse in women than in men, although there are inconsistencies in studies depending on the study design, study population and the disease explored. Women have been reported to have worse adherence than men with treatment for symptomatic heart failure,[45] lipid disorders,[46] and hypertension.[47;48] Adults report several reasons for failure to take their medications as prescribed. In a prospective study of 821 patients filling antihypertensive medications at community pharmacies, 56% of patients reported that the single most common reason they did not take their medications as prescribed was forgetfulness. Other commonly cited reasons included not being convinced of the need for and value of therapy, hate taking medication and do not want to become dependent on medications. Interestingly, only 6% reported side effects and only 2% reported medications as too expensive as reasons for not taking medications.[49] Another challenge is white coat adherence: patients have progressive decline in drug adherence over weeks after being prescribed medications followed by a sudden improvement in drug adherence during the few days preceding the medical visit.[50] The increase in adherence right before the clinic visit may result in control of disease at the time of the visit but not reflect ongoing disease control; thus, patients and health care providers may derive a false sense of security regarding effectiveness of the treatment.

It is important for physicians and other healthcare providers to consider low medication adherence as a factor contributing to poor BP control, to communicate with their patients about the importance of medication adherence in light of patient-specific barriers (i.e. tailored approach), and to consider strategies upfront that lessen the effect of barriers on medication adherence and actively engage patients in adhering to their prescribed medications[51]. Despite the negative impact of low adherence on disease control, healthcare providers do not routinely assess adherence in clinical practice. This may because they doubt that low adherence is a cause of uncontrolled BP, are uncertain about quantifying adherence, or are unaware of modifiable factors that could be targeted for intervention in routine clinical practice.[52–55] Advances in adherence research have addressed many of these concerns.

There are several methods available for assessing medication adherence including direct methods (such as bioassays and biomarkers and directly observed therapy) and indirect methods (including electronic monitors such as medication event monitoring systems caps, pill counts, self-report and pharmacy fill rates). Although there is no gold standard for assessing adherence to chronic disease medications and each method has its strengths and weaknesses, self-report tools and pharmacy fill rates are increasingly being used in clinical and research settings.[56] More recent studies have identified modifiable determinants of low adherence and the association of adherence measured with these indirect tools on BP control and CV events. One such study is the Cohort Study of Medication Adherence in Older Adults (CoSMO).

The CoSMO was a prospective cohort study of factors associated with antihypertensive medication adherence and CVD outcomes in elderly community-dwelling women and men, a population with high burden of hypertension. The study design, response rates, and baseline characteristics have been published previously[22]. In brief, women and men aged 65 years or older with essential hypertension were randomly selected from the roster of a large

managed care organization. In total, 2,194 participants were enrolled[22]. The participants were followed for nearly four years to identify CVD events and mortality. The study was designed to assess risk factors for low antihypertensive medication adherence, explore differences across age, gender, and race subgroups, and determine the relationship of adherence with BP control and cardiovascular outcomes over time.

Antihypertensive medication adherence was assessed with the self-report Morisky Medication Adherence Scale (MMAS) and the objective pharmacy fill Medication Possession Ratio-MPR.[53;56] Low adherence was defined as a MMAS score < 6; low or non-persistent MPR was defined as <0.80. BP data were abstracted from outpatient electronic medical records; uncontrolled BP was defined as systolic or diastolic BP ≥140 or 90 mmHg, respectively.[22] Overall, the mean age of the participants at baseline was 75 years, 58.8% were women, 30.7% were black, 14.1% had low MMAS and 27.0% had nonpersistent MPR, 33.7% had uncontrolled BP and 62.8% had hypertension for more than 10 years. Women enrolled in the study, compared to men, were significantly older, less likely to be married, less likely to have hypertension for more than 10 years, and have higher cholesterol levels and a lower comorbidity score; women and participants with duration of hypertension > 10 years were more likely to have uncontrolled BP.[22] Women compared to men had a nonsignificant trend for worse adherence by self-report (14.9% versus 13.0%, respectively) and by pharmacy fill (27.5% versus 26.4%, respectively). In addition, blacks compared to whites had significantly lower adherence to antihypertensive medication as assessed by MMAS and MPR.[22]

Results from the CoSMO study have provided important data and insights regarding assessment of medication adherence and its association with meaningful biological markers such as BP, understanding of meaningful change in self-reported adherence, and associations with adverse cardiovascular outcomes. Low versus high adherence by both self-reported (MMAS) and pharmacy refill (MPR) measures was significantly associated with uncontrolled BP cross-sectionally[22] and over time[57] ($p<0.05$ for each comparison). A 2-point change in MMAS (eg, score change from 7 to 5) has been identified as a meaningful change in adherence[58]; a 2-point decline in MMAS was associated with a 1.68 OR (95% CI, 1.01–2.80) for uncontrolled BP among women and men with controlled BP before the decline.[54]

After multivariable adjustment, factors associated with low medication adherence (using both MMAS and MPR) in older women and men were identified in CoSMO: low health-related quality of life (both physical and mental summary component scales)[59]; depressive symptoms (with a stronger association in women compared with men)[60]; low social support (borderline significance); occurrence of stressful life events among women and men with low coping skills (Of note, specific life events with strongest association with low adherence were change in health or behavior of family member, change in financial state, change in eating or sleeping habits, change in recreation, social and church activities).[61] The associations of low antihypertensive medication adherence with complementary and alternative medicine (CAM) use were 1.56 (95% CI, 1.14–2.15) and 0.95 (95% CI, 0.70–1.29) among blacks and whites, respectively.[62] Subsequent analyses regarding CAM use revealed nonsignificant trends in higher rates of uncontrolled BP (41.7% versus 39.1% in

CAM versus no CAM users) and cardiovascular events (11.7% versus 8.2% in CAM versus no CAM users) among blacks; no trends with CAM use and outcomes were identified among whites.

When assessing sex differences in the barriers and determinants of low self-reported medication adherence in older adults, the following sex differences were identified:[63]

- Women and men: medication costs and practicing fewer than 2 lifestyle modifications for BP control were associated with low adherence
- Women but not men: dissatisfaction with communication with their health care providers and presence of depressive symptoms were associated with low adherence
- Men but not women: reduced sexual functioning and body mass index greater than or equal to 25 were associated with low adherence.

In looking at factors associated with decline in self-reported adherence over time, several factors were significantly associated with at least a 2-point decline in self-reported adherence over 2 years of follow up. Depressive symptoms (OR, 1.84; 95% CI, 1.20–2.82) and high stressful life events score (OR, 1.68; 95% CI, 1.19–2.38) were associated with higher ORs for decline in medication adherence. Women (OR, 0.61; 95% CI, 0.42–0.88); being married (OR, 0.68; 95% CI, 0.47–0.98); and calcium channel blocker use (OR, 0.68; 95% CI, 0.48–0.97) were protective of decline in adherence.[54]

Overall, we identified several potentially modifiable factors to address low medication adherence in older women and men: use of CAM in blacks, low use of lifestyle modifications, depressive symptoms, low social support, low health related quality of life, sexual dysfunction in men, antihypertensive medication class. Other factors, which are not modifiable but could be important in identifying patients at risk for low adherence and subsequently uncontrolled disease include gender, race, culture, marital status, and occurrence of stressful life events. Health care providers should consider these factors in older women and men with hypertension who are at risk for low medication adherence and uncontrolled disease.

In the most recent analyses, associations of self-report and pharmacy refill adherence adherence with follow up CVD event rate were assessed. Compared with their counterparts with high adherence, those with low adherence to antihypertensive medication (MPR <0.5), had a nearly 2-fold higher risk of a CVD event over a median follow-up of 3.8 years (1.87 [95% CI, 1.06–3.30]); there was no association between adherence measured by MMAS-8 and CVD.[57] For pharmacy refill adherence, these findings are similar to prior studies revealing that pharmacy refill adherence is associated with lower risk of long-term adverse clinical outcomes in patients treated for hypertension[23–27;64]. However, fewer studies have contrasted pharmacy refill versus self-reported antihypertensive medication adherence on CVD outcomes. In fully adjusted models stratified by gender, the association between low versus high pharmacy refill adherence and cardiovascular events was stronger in women than in men, hazard ratio 2.61 (95% CI, 1.26–5.39) in women versus hazard ratio 1.19 (95%

CI, 0.47–3.04) in men.[57] There was no association with self-report MMAS-8 adherence and cardiovascular events when stratified by sex.

To date, this work supports that valid tools exist for assessing adherence to antihypertensive medications that may be suitable for clinical practice and research settings. The adherence measures are associated with BP control (pharmacy refill and self-report) and cardiovascular events (pharmacy refill but not self-report). Having information on both self-report and pharmacy refill adherence behavior may benefit physicians and other healthcare providers. During clinic visits, self-report tools provide a rapid way to identify which patients are adhering to antihypertensive medications, to obtain important information on key barriers to adherence that can be targeted for interventions in the short term, and to monitor change in adherence[54]. Pharmacy refill measures like MPR or proportion of days covered can be used to identify those not filling prescriptions over time and assess risk of adverse outcomes in the long-term. Together, the objective and self-reported adherence measures provide complementary information that can guide appropriate engagement of patients and providers in the management of high BP and other chronic conditions. Pharmacy refill measures may be particularly important for research studies and population management projects given the association between this measure and CVD events.[57] Given resources are limited in healthcare settings and the need to tailor interventions to address patient-specific barriers and challenges, it is important to identify women and men who are likely to benefit the most from interventions to improve adherence and disease control. Therefore, women and men who are not at treatment goal, have multiple comorbidities and medications, experience side effects or barriers and/or are high utilizers of hospital and emergency services may signal a greater need for adherence interventions than those without these characteristics. Future research is needed to identify, refine and evaluate interventions to improve and sustain high adherence to medications and to achieve disease control and reduce adverse events.

Conclusion

Hypertension is an ongoing clinical and public health challenge associated with increased cardiovascular risk in girls and women. Poor adherence to healthy lifestyles and prescribed medications is a growing concern because of the established link of adherence with disease control and clinical outcomes. Efforts to identify girls and women at risk for poor adherence and uncontrolled hypertension and to address barriers to adherence to health behaviors have the potential for substantive impact on reducing CVD and improving heart disease survival in women.

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