

THEME A: Out of Office Blood Pressure Monitoring

Hermida RC, Ayala DE, Fernández JR, Calvo C. Chronotherapy improves blood pressure control and reverts the nondipper pattern in patients with resistant hypertension. Hypertension. 2008 Jan;51(1):69-76. Epub 2007 Oct 29

Therapeutic strategies in resistant hypertension include adding another drug or changing drugs in search for a better synergic combination. Most patients, however, receive all of their drugs in a single morning dose. We have evaluated the impact on the circadian pattern of blood pressure on modifying the time of treatment without increasing the number of prescribed drugs. We studied 250 hypertensive patients who were receiving 3 antihypertensive drugs in a single morning dose. Patients were randomly assigned to 1 of 2 groups according to the modification in their treatment strategy: changing 1 of the drugs but keeping all 3 in the morning or the same approach but administering the new drug at bedtime. Blood pressure was measured for 48 hours before and after 12 weeks of treatment. There was no effect on ambulatory blood pressure when all of the drugs were taken on awakening. The baseline prevalence of nondipping (79%) was slightly increased after treatment (86%; $P=0.131$). The ambulatory blood pressure reduction was statistically significant (9.4/6.0 mm Hg for systolic/diastolic blood pressure; $P<0.001$) with 1 drug at bedtime. This reduction was larger in the nocturnal than in the diurnal mean of blood pressure. Thus, whereas only 16% of the patients in this group were dippers at baseline, 57% were dippers after therapy ($P<0.001$). Results indicate that, in resistant hypertension, time of treatment may be more important for blood pressure control and for the proper modeling of the circadian blood pressure pattern than just changing the drug combination.

Hermida RC. Ambulatory blood pressure monitoring in the prediction of cardiovascular events and effects of chronotherapy: rationale and design of the MAPEC study. Chronobiol Int. 2007; 24(4):749-75.

Ambulatory blood pressure (BP) measurements (ABPM) correlate more closely with target organ damage and cardiovascular events than clinical cuff measurements. ABPM reveals the significant circadian variation in BP, which in most individuals presents a morning increase, small post-prandial decline, and more extensive lowering during nocturnal rest. However, under certain pathophysiological conditions, the nocturnal BP decline may be reduced (non-dipper pattern) or even reversed (riser pattern). This is clinically relevant because the non-dipper and riser circadian BP patterns constitute a risk factor for left ventricular hypertrophy, microalbuminuria, cerebrovascular disease, congestive heart failure, vascular dementia, and myocardial infarction. Hence, there is growing interest in how to best tailor and individualize the treatment of hypertension according to the specific circadian BP pattern of each patient. All previous trials that have demonstrated an increased cardiovascular risk in non-dipper as compared to dipper patients have relied on the prognostic significance of a single ABPM baseline profile from each participant without accounting for possible changes in the BP pattern during follow-up. Moreover, the potential benefit (i.e., reduction in cardiovascular risk) associated with the normalization of the circadian BP variability (conversion from non-

dipper to dipper pattern) from an appropriately envisioned treatment strategy is still a matter of debate. Accordingly, the MAPEC (Monitorización Ambulatoria de la Presión Arterial y Eventos Cardiovasculares, i.e., Ambulatory Blood Pressure Monitoring and Cardiovascular Events) study was designed to investigate whether the normalization of the circadian BP profile toward more of a dipper pattern by chronotherapeutic strategies (i.e., specific timing during the 24 h of BP-lowering medications according to the 24 h BP pattern) reduces cardiovascular risk. The prospective MAPEC study investigates 3,000 diurnally active men and women ≥ 18 yrs of age. At inclusion, BP and wrist activity are measured for 48 h. The initial evaluation also includes a detailed medical history, an electrocardiogram, and screening laboratory blood and urine tests. The same evaluation procedure is scheduled yearly or more frequently (quarterly) if treatment adjustment is required for BP control. Cardiovascular morbidity and mortality are thus evaluated on the basis of changes in BP during follow-up. The MAPEC study, now on its fourth year of follow-up, investigates the potential decrease in cardiovascular, cerebrovascular, and renal risk from the proper modeling of the circadian BP profile by the timed administration (chronotherapy) of antihypertensive medication, beyond the reduction of clinic-determined daytime or ABPM-determined 24 h mean BP levels

Matsui Y, Eguchi K, Ishikawa J, Hoshida S, Shimada K, Kario K. Subclinical arterial damage in untreated masked hypertensive subjects detected by home blood pressure measurement. Am J Hypertens. 2007 Apr;20(4):385-91.

BACKGROUND: Masked hypertension (MHT: normal office blood pressure [BP] + elevated BP out of the office) is a significant predictor of target organ damage and cardiovascular disease. The purpose of this study was to investigate the subclinical arterial damage in unmedicated subjects with MHT detected by home BP measurement. **METHODS:** We recruited 282 subjects not taking antihypertensive medication, who had at least one of the following five cardiovascular risk factors: high BP, hyperlipidemia, diabetes mellitus, current smoking, and chronic kidney disease. Furthermore, we classified them into four groups (normotension [NT], white-coat hypertension [WCHT], MHT, and sustained hypertension [SHT]) by office BP (140/90 mm Hg) and home BP (135/85 mm Hg) measurements. Arterial damage was evaluated by measuring carotid intima-media thickness (IMT) and brachial-ankle pulse wave velocity (baPWV). **RESULTS:** Subjects with MHT had a higher prevalence of habitual alcohol drinkers than the other groups, and higher pulse rates at home than those with NT and WCHT. After adjustment for covariates, carotid IMT was the highest in MHT among the four groups (mean: 1.01 v 0.83 mm for NT, 0.86 mm for WCHT, and 0.91 mm for SHT, all $P < .01$). The baPWV was also significantly higher in MHT than NT and WCHT (mean: 1940 v 1663 and 1733 cm/sec, all $P < .01$), whereas the difference between MHT and SHT (2023 cm/sec) was not significant. **CONCLUSIONS:** This study shows that masked hypertensives detected by home BP are at higher risk for increased arterial damage than normotensives or white-coat hypertensives, and potentially than sustained hypertensives.

Larkin KT, Schauss SL, Elnicki DM, Goodie JL. Detecting white coat and reverse white coat effects in clinic settings using measures of blood pressure habituation in the clinic and patient self-monitoring of blood pressure. J Hum Hypertens. 2007 Jul; 21(7):516-24. Epub 2007 Mar 15.

To examine the utility of blood pressure (BP) habituation within and across multiple clinic visits and patient-determined home BP monitoring for detecting white coat (WCE) and reverse white coat effects (RWCE) commonly observed in medical settings, 54 patients undergoing evaluation for hypertension in an internal medicine group practice were categorized according to the magnitude of differences between systolic BP (SBP) and diastolic BP (DBP) obtained in the clinic and through ambulatory BP monitoring. BPs were measured four times during three separate clinic visits, during a 1-week home BP monitoring period, and during a single 24-h ambulatory monitoring period. Patients whose mean clinic and average daytime BPs were within ± 5 mm Hg were categorized as having stable BP; patients whose clinic BPs were >5 mm Hg of their daytime BPs were categorized as showing a WCE and patients whose average daytime BPs were >5 mm Hg of their clinic BPs were categorized as showing a RWCE. Results revealed that degree of habituation occurring between the first and third clinic visits significantly predicted magnitude of both the WCE and RWCE for SBP, with greater habituation being associated with the WCE and lesser habituation associated with the RWCE. Greater SBP habituation within clinic visits was associated with the WCE for SBP and greater DBP habituation within clinic visits was associated with the WCE for DBP. Lesser DBP habituation within clinic visits was associated with the RWCE for both SBP and DBP. Home BP monitoring did not contribute to predicting either WCE or RWCE.

Stergiou GS, Argyraki KK, Moysakakis I, Mastorantonakis SE, Achimastos AD, Karamanos VG, Roussias LG. Home blood pressure is as reliable as ambulatory blood pressure in predicting target-organ damage in hypertension. Am J Hypertens. 2007 Jun; 20(6):616-21.

BACKGROUND: Our objective was to assess the value of home blood pressure (BP) monitoring in comparison to office BP measurements and ambulatory monitoring in predicting hypertension-induced target-organ damage. **METHODS:** Sixty-eight untreated patients with hypertension with at least two routine prestudy office visits were included (mean age, 48.6 \pm 9.1 [SD] years; 50 men). Office BP was measured in two study visits, home BP was measured for 6 workdays, and ambulatory BP was monitored for 24 h. All BP measurements were obtained using validated electronic devices. Target-organ damage was assessed by measuring the echocardiographic left-ventricular mass index (LVMI), urinary albumin excretion rate (AER) in two overnight urine collections, and carotid-femoral pulse-wave velocity (PWV) (Complior device; Colson, Garges-les-Gonesse, Paris, France). **RESULTS:** The correlation coefficients of LVMI with office BP were 0.24/0.15 (systolic/diastolic), with home BP 0.35/0.21 (systolic, $P < .01$), and with 24-h ambulatory BP 0.23/0.19, awake 0.21/0.16, and asleep 0.28/0.26 (asleep, both $P < .05$). The correlation coefficients of AER with office BP were 0.24/0.31 (diastolic, $P < .05$), with home BP 0.28/0.26 (both $P < .05$), and with 24-h ambulatory BP 0.25/0.24, awake

0.24/0.25 (diastolic, $P < .05$), and asleep 0.26/0.18 (systolic, $P < .05$). There was a trend for negative correlations between PWV and diastolic BP measurements (not significant). In multiple-regression models assessing independent predictors of each of the three indices of target-organ damage, systolic home BP and age were the only independent predictors of increased LVMI that reached borderline statistical significance. CONCLUSIONS: These data suggest that home BP is as reliable as ambulatory monitoring in predicting hypertension-induced target-organ damage, and is superior to carefully taken office measurements.

THEME B: Nonpharmacologic Treatments for Hypertension

Artinian NT, Flack JM, Nordstrom CK, Hockman EM, Washington OG, Jen KL, Fathy M. Effects of nurse-managed telemonitoring on blood pressure at 12-month follow-up among urban African Americans. Nurs Res. 2007 Sep-Oct;56(5):312-22.

BACKGROUND: Nearly one in three adults in the United States has hypertension. Hypertension is one of the largest risk factors for cardiovascular diseases, and it is growing in prevalence, especially among African Americans. OBJECTIVES: To test the hypothesis that individuals who participate in usual care (UC) plus blood pressure (BP) telemonitoring (TM) will have a greater reduction in BP from baseline to 12-month follow-up than would individuals who receive UC only. METHODS: A two-group, experimental, longitudinal design with block stratified randomization for antihypertensive medication use was used. African Americans with hypertension were recruited through free BP screenings offered in the community. Data were collected through a structured interview and brief physical exam. Cross tabs, repeated measures analysis of variance, and independent t tests were used to analyze the study's hypothesis. RESULTS: The TM intervention group had a greater reduction in systolic BP (13.0 mm Hg) than the enhanced UC group (7.5 mm Hg; $t = -2.09$, $p = .04$) from baseline to the 12-month follow-up. Although the TM intervention group had a greater reduction in diastolic BP (6.3 mm Hg) compared with the enhanced UC group (4.1 mm Hg), the differences were not statistically significant ($t = -1.56$, $p = .12$). DISCUSSION: Telemonitoring of BP resulted in clinically and statistically significant reductions in systolic BP over a 12-month period; if maintained over a longer period of time, the reductions could improve care and outcomes significantly for African Americans with hypertension.

Wang L, Gaziano JM, Liu S, Manson JE, Buring JE, Sesso HD. Whole- and refined-grain intakes and the risk of hypertension in women. Am J Clin Nutr. 2007 Aug;86(2):472-9.

BACKGROUND: Prospective studies linking whole- and refined-grain intakes with the risk of hypertension, a major cardiovascular disease risk factor, remain limited. OBJECTIVE: We aimed to determine whether baseline intake of whole or refined grains is associated with subsequent development of hypertension. DESIGN: We conducted a prospective cohort study in 28 926 female US health professionals aged ≥ 45 y who

were free of baseline cardiovascular disease, cancer, and hypertension in 1992. Baseline whole- and refined-grain intakes were assessed from semiquantitative food-frequency questionnaires. We identified 8722 incident cases of hypertension from annual questionnaires during 10 y of follow-up. RESULTS: After adjustment for known hypertension risk factors, the relative risks (RRs) (and 95% CIs) of incident hypertension were 1.00 (reference), 0.96 (0.89, 1.03), 0.95 (0.88, 1.02), 0.92 (0.85, 0.99), and 0.89 (0.82, 0.97) across the increasing quintiles of baseline whole-grain intake (P for trend = 0.007). When functional cutoffs were used, women who consumed 0.5 to <1, 1 to <2, 2 to <4, and ≥ 4 whole-grain servings/d had multivariate RRs (95% CIs) of 0.93 (0.87, 1.00), 0.93 (0.87, 0.99), 0.92 (0.85, 0.99), and 0.77 (0.66, 0.89), respectively, compared with those who consumed <0.5 whole-grain servings/d. In contrast, refined-grain intake was not associated with the risk of hypertension. The multivariate RRs of hypertension across the increasing quintiles of refined-grain intake were 1.00, 0.97, 0.94, 0.99, and 0.97 (P for trend = 0.80). CONCLUSION: Higher whole-grain intake was associated with a reduced risk of hypertension in middle-aged and older women, which suggests a potential role for increasing whole-grain intake in the primary prevention of hypertension and its cardiovascular complications.

Flachskampf FA, Gallasch J, Gefeller O, Gan J, Mao J, Pfahlberg AB, Wortmann A, Klinghammer L, Pfleiderer W, Daniel WG. Randomized trial of acupuncture to lower blood pressure. *Circulation*. 2007 Jun 19;115(24):3121-9. Epub 2007 Jun 4.

BACKGROUND: Arterial hypertension is a prime cause of morbidity and mortality in the general population. Pharmacological treatment has limitations resulting from drug side effects, costs, and patient compliance. Thus, we investigated whether traditional Chinese medicine acupuncture is able to lower blood pressure. METHODS AND RESULTS: We randomized 160 outpatients (age, 58 \pm 8 years; 78 men) with uncomplicated arterial hypertension in a single-blind fashion to a 6-week course of active acupuncture or sham acupuncture (22 sessions of 30 minutes' duration). Seventy-eight percent were receiving antihypertensive medication, which remained unchanged. Primary outcome parameters were mean 24-hour ambulatory blood pressure levels after the treatment course and 3 and 6 months later. One hundred forty patients finished the treatment course (72 with active treatment, 68 with sham treatment). There was a significant (P<0.001) difference in posttreatment blood pressures adjusted for baseline values between the active and sham acupuncture groups at the end of treatment. For the primary outcome, the difference between treatment groups amounted to 6.4 mm Hg (95% CI, 3.5 to 9.2) and 3.7 mm Hg (95% CI, 1.6 to 5.8) for 24-hour systolic and diastolic blood pressures, respectively. In the active acupuncture group, mean 24-hour ambulatory systolic and diastolic blood pressures decreased significantly after treatment by 5.4 mm Hg (95% CI, 3.2 to 7.6) and 3.0 mm Hg (95% CI, 1.5 to 4.6), respectively. At 3 and 6 months, mean systolic and diastolic blood pressures returned to pretreatment levels in the active treatment group. CONCLUSIONS: Acupuncture according to traditional Chinese medicine, but not sham acupuncture, after 6 weeks of treatment significantly lowered mean 24-hour ambulatory blood pressures; the effect disappeared after cessation of acupuncture treatment.

Welty FK, Lee KS, Lew NS, Zhou JR. Effect of soy nuts on blood pressure and lipid levels in hypertensive, prehypertensive, and normotensive postmenopausal women. Arch Intern Med. 2007 May 28;167(10):1060-7

BACKGROUND: Epidemiologic studies suggest a low incidence of cardiovascular disease in populations that consume dietary soy. For people aged 40 to 70 years, each increment of 20 mm Hg in systolic blood pressure (BP) or 10 mm Hg in diastolic BP doubles the risk of cardiovascular disease for BPs of 115/75 to 185/115 mm Hg. **METHODS:** To determine the effect of soy nuts on systolic and diastolic BP and lipid levels, 60 healthy postmenopausal women were randomized in a crossover design to a Therapeutic Lifestyle Changes (TLC) diet alone and a TLC diet of similar energy, fat, and protein content in which soy nuts (containing 25 g of soy protein and 101 mg of aglycone isoflavones) replaced 25 g of non-soy protein. Each diet was followed for 8 weeks. **RESULTS:** Compared with the TLC diet alone, the TLC diet plus soy nuts lowered systolic and diastolic BP 9.9% and 6.8%, respectively, in hypertensive women (systolic BP \geq 140 mm Hg) and 5.2% and 2.9%, respectively, in normotensive women (systolic BP $<$ 120 mm Hg). Further subdivision of normotensive women revealed that systolic and diastolic BPs were lowered 5.5% and 2.7%, respectively, in prehypertensive women (systolic BP of 120-139 mm Hg) and 4.5% and 3.0%, respectively, in normotensive women. Soy nut supplementation lowered low-density lipoprotein cholesterol and apolipoprotein B levels 11% and 8% ($P = .04$ for both), respectively, in hypertensive women but had no effect in normotensive women. **CONCLUSIONS:** Substituting soy nuts for nonsoy protein in a TLC diet improves BP and low-density lipoprotein cholesterol levels in hypertensive women and BP in normotensive postmenopausal women. These findings may explain a cardioprotective effect of soy.

Burke V, Beilin LJ, Cutt HE, Mansour J, Williams A, Mori TA. A lifestyle program for treated hypertensives improved health-related behaviors and cardiovascular risk factors, a randomized controlled trial. J Clin Epidemiol. 2007 Feb;60(2):133-41. Epub 2006 Sep 28.

OBJECTIVE: To assess effects of a cognitively based program on health-related behaviors and cardiovascular risk factors in overweight drug-treated hypertensives. **STUDY DESIGN AND SETTING:** In a clinical trials center, volunteers, recruited by advertisement, were randomized to usual care ($N=118$) or to a 4-month program ($N=123$) incorporating weight loss; a low-sodium diet, high in fruit, vegetables, and fish; and increased physical activity. Diet, physical activity, weight, blood lipids, glucose, and insulin were measured at 4 and 16 months. **RESULTS:** Ninety-eight usual care and 106 program participants completed the 4-month assessment; 90 and 102, respectively, completed follow-up. Using intention-to-treat analysis, relative to usual care, net changes with the program at 4 months were as follows: dietary fat (-2.6% energy; $P<0.001$); sodium (-290mg/d; $P=0.004$); energy (-313mJ/d; $P=0.005$); fish (+2.1 serves/wk; $P<0.001$); vegetables (+3.0 serves/wk; $P<0.001$); physical activity (+37min/wk;

P=0.004); weight (-2.8kg; P<0.001); waist girth (-3.1cm; P<0.001); total cholesterol (-0.2mmol/L; P=0.017); and triacylglycerols (-0.12mmol/L; P=0.002). One year later, net changes included dietary fat (-2.2% energy; P<0.001); sodium (-150mg/d; P=0.029); fish (+2.0 serves/wk; P<0.001); vegetables (+4.3 serves/wk; P<0.001); weight (-2.5kg; P=0.001); waist girth (-3.1cm; P<0.001); high-density lipoprotein cholesterol (+0.03mmol/L; P=0.031). CONCLUSION: Improvements in behaviors and risk factors, several maintained long term, suggest the potential for long-term benefits in hypertensives.

Taubert D, Roesen R, Lehmann C, Jung N, Schömig E. Effects of low habitual cocoa intake on blood pressure and bioactive nitric oxide: a randomized controlled trial. JAMA. 2007 Jul 4;298(1):49-60.

CONTEXT: Regular intake of cocoa-containing foods is linked to lower cardiovascular mortality in observational studies. Short-term interventions of at most 2 weeks indicate that high doses of cocoa can improve endothelial function and reduce blood pressure (BP) due to the action of the cocoa polyphenols, but the clinical effect of low habitual cocoa intake on BP and the underlying BP-lowering mechanisms are unclear. OBJECTIVE: To determine effects of low doses of polyphenol-rich dark chocolate on BP. DESIGN, SETTING, AND PARTICIPANTS: Randomized, controlled, investigator-blinded, parallel-group trial involving 44 adults aged 56 through 73 years (24 women, 20 men) with untreated upper-range prehypertension or stage 1 hypertension without concomitant risk factors. The trial was conducted at a primary care clinic in Germany between January 2005 and December 2006. INTERVENTION: Participants were randomly assigned to receive for 18 weeks either 6.3 g (30 kcal) per day of dark chocolate containing 30 mg of polyphenols or matching polyphenol-free white chocolate. MAIN OUTCOME MEASURES: Primary outcome measure was the change in BP after 18 weeks. Secondary outcome measures were changes in plasma markers of vasodilative nitric oxide (S-nitrosoglutathione) and oxidative stress (8-isoprostane), and bioavailability of cocoa polyphenols. RESULTS: From baseline to 18 weeks, dark chocolate intake reduced mean (SD) systolic BP by -2.9 (1.6) mm Hg (P < .001) and diastolic BP by -1.9 (1.0) mm Hg (P < .001) without changes in body weight, plasma levels of lipids, glucose, and 8-isoprostane. Hypertension prevalence declined from 86% to 68%. The BP decrease was accompanied by a sustained increase of S-nitrosoglutathione by 0.23 (0.12) nmol/L (P < .001), and a dark chocolate dose resulted in the appearance of cocoa phenols in plasma. White chocolate intake caused no changes in BP or plasma biomarkers. CONCLUSIONS: Data in this relatively small sample of otherwise healthy individuals with above-optimal BP indicate that inclusion of small amounts of polyphenol-rich dark chocolate as part of a usual diet efficiently reduced BP and improved formation of vasodilative nitric oxide. TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT00421499.

Ambühl PM, Tissot AC, Fulurija A, Maurer P, Nussberger J, Sabat R, Nief V, Schellekens C, Sladko K, Roubicek K, Pfister T, Rettenbacher M, Volk HD, Wagner F,

Müller P, Jennings GT, Bachmann MF. A vaccine for hypertension based on virus-like particles: preclinical efficacy and phase I safety and immunogenicity. J Hypertens. 2007 Jan; 25(1):63-72.

BACKGROUND: Despite the availability of efficacious drugs, the success of treating hypertension is limited by patients' inconsistent drug intake. Immunization against angiotensin II may offer a valuable alternative to conventional drugs for the treatment of hypertension, because vaccines induce relatively long-lasting effects and do not require daily dosing. Here we describe the preclinical development and the phase I clinical trial testing of a virus-like particle (VLP)-based antihypertensive vaccine. **METHODS AND RESULTS:** An angiotensin II-derived peptide was conjugated to the VLP Qbeta (AngQb). AngQb was highly immunogenic in mice and rats. To test for efficacy, spontaneously hypertensive rats (SHR) were immunized with 400 microg AngQb or VLP alone. Group mean systolic blood pressure (SBP) was reduced by up to 21 mmHg (159 +/- 2 versus 180 +/- 5 mmHg, $P < 0.001$), and total angiotensin II levels (antibody-bound and free) were increased ninefold (85 +/- 20 versus 9 +/- 1 pmol/l, $P = 0.002$) compared with VLP controls. SHR treated with the angiotensin-converting enzyme (ACE) inhibitor ramipril (1 mg/kg per day by mouth) reached an SBP of 155 +/- 2 mmHg. Twelve healthy volunteers of a placebo-controlled randomized phase I trial were injected once with 100 microg AngQb. Angiotensin II-specific antibodies were raised in all subjects (100% responder rate) and AngQb was well tolerated. **CONCLUSIONS:** AngQb reduces blood pressure in SHR to levels obtained with an ACE inhibitor, and is immunogenic and well tolerated in humans. Therefore, vaccination against angiotensin II has the potential to become a useful antihypertensive treatment providing long-lasting effects and improving patient compliance.

THEME C: Psychosocial Barriers to Hypertension Control

Roumie CL, Elasy TA, Wallston KA, Pratt S, Greevy RA, Liu X, Alvarez V, Dittus RS, Speroff T. Clinical inertia: a common barrier to changing provider prescribing behavior. Jt Comm J Qual Patient Saf. 2007 May;33(5):277-85.

BACKGROUND: A cross-sectional content analysis nested within a randomized, controlled trial was conducted to collect information on provider responses to computer alerts regarding guideline recommendations for patients with suboptimal hypertension care. **METHODS:** Participants were providers who cared for 1,017 patients with uncontrolled hypertension on a single antihypertensive agent within Veterans Affairs primary care clinics. All reasons for action or inaction were sorted into a framework to explain the variation in guideline adaptation. **RESULTS:** The 184 negative provider responses to computer alerts contained explanations for not changing patient treatment; 76 responses to the alerts were positive, that is, the provider was going to make a change in antihypertensive regimen. The negative responses were categorized as: inertia of practice (66%), lack of agreement with specific guidelines (5%), patient-based factors (17%), environmental factors (10%), and lack of knowledge (2%). Most of the 135 providers classified as inertia of practice indicated, "Continue current medications and I will discuss at the next visit." The median number of days until the next visit was 45 days

(interquartile range, 29 to 78 days). DISCUSSION: Clinical inertia was the primary reason for failing to engage in otherwise indicated treatment change in a subgroup of patients. A framework was provided as a taxonomy for classification of provider barriers.

Kressin NR, Wang F, Long J, Bokhour BG, Orner MB, Rothendler J, Clark C, Reddy S, Kozak W, Kroupa LP, Berlowitz DR. Hypertensive patients' race, health beliefs, process of care, and medication adherence. J Gen Intern Med. 2007 Jun;22(6):768-74. Epub 2007 Mar 16

BACKGROUND: African Americans have higher rates of hypertension and worse blood pressure (BP) control than Whites, and poorer medication adherence may contribute to this phenomenon. We explored associations among patients' race, self-reported experiences with clinicians, attitudes and beliefs about hypertension, and ultimately, medication adherence, among a sample with no racial disparities in BP control, to determine what lessons we could learn from patients and providers in this setting. METHODS: We recruited 793 White and African-American (58%) patients previously diagnosed with hypertension from 3 VA medical centers to participate in survey assessments of each of the above dimensions, subsequent to a primary care clinic visit. RESULTS: African-American patients' providers were significantly more active in advising and counseling about hypertension care and medication adherence. African-American patients indicated greater knowledge or heightened awareness of the importance of controlling their BP, but there were no race differences on a summary adherence measure. In multivariate models modeling medication adherence, race was not significant, but having been told to split one's pills, believing one's BP continues to be high, and having one's provider discuss things to do to make it easier to take BP medications were each significantly associated with worse adherence, whereas having more confidence in one's ability to take BP medications as prescribed was associated with better adherence (all p's < or = .02). CONCLUSION: When both physicians and patients take BP management seriously, disparities in BP adherence and control may be reduced.

Hyre AD, Krousel-Wood MA, Muntner P, Kawasaki L, DeSalvo KB Prevalence and predictors of poor antihypertensive medication adherence in an urban health clinic setting. K Clin Hypertens (Greenwich). 2007 Mar;9(3):179-86.

Poor medication adherence may contribute to low hypertension control rates. In 2005, 295 hypertensive patients who reported taking antihypertensive medications were administered a telephone questionnaire including an 8-item scale assessing medication adherence. Overall, 35.6%, 36.0%, and 28.4% of patients were determined to have good, medium, and poor medication adherence, respectively. After multivariable adjustment, adults younger than 50 years and 51 to 60 years were 1.39 (95% confidence interval [CI], 0.56-3.42) and 1.53 (95% CI, 0.64-3.66), respectively, times more likely to be less adherent when compared with their counterparts who were older than 60 years. Black adults and men were 4.30 (95% CI, 1.06-17.5) and 2.45 (95% CI, 1.04-5.78) times more likely to be less adherent, respectively. Additionally, caring for dependents, an initial

diagnosis of hypertension within 10 years, being uncomfortable about asking the doctor questions, and wanting to spend more time with the doctor if possible were associated with poor medication adherence. The current study identified a set of risk factors for poor antihypertensive medication adherence in the urban setting.

THEME D: Antihypertensive Therapy Risks and Benefits

Fagard RH, Staessen JA, Thijs L, Celis H, Bulpitt CJ, de Leeuw PW, Leonetti G, Tuomilehto J, Yodfat Y. On-treatment diastolic blood pressure and prognosis in systolic hypertension. Arch Intern Med. 2007 Sep 24;167(17):1884-91

BACKGROUND: It has been suggested that low diastolic blood pressure (BP) while receiving antihypertensive treatment (hereinafter called on-treatment BP) is harmful in older patients with systolic hypertension. We examined the association between on-treatment diastolic BP, mortality, and cardiovascular events in the prospective placebo-controlled Systolic Hypertension in Europe Trial. **METHODS:** Elderly patients with systolic hypertension were randomized into the double-blind first phase of the trial, after which all patients received active study drugs (phase 2). We assessed the relationship between outcome and on-treatment diastolic BP by use of multivariate Cox regression analysis during receipt of placebo (phase 1) and during active treatment (phases 1 and 2). **RESULTS:** Rates of noncardiovascular mortality, cardiovascular mortality, and cardiovascular events were 11.1, 12.0, and 29.4, respectively, per 1000 patient-years with active treatment (n = 2358) and 11.9, 12.6, and 39.0, respectively, with placebo (n = 2225). Noncardiovascular mortality, but not cardiovascular mortality, increased with low diastolic BP with active treatment ($P < .005$) and with placebo ($P < .05$); for example, hazard ratios for lower diastolic BP, that is, 65 to 60 mm Hg, were, respectively, 1.15 (95% confidence interval, 1.00-1.31) and 1.28 (95% confidence interval, 1.03-1.59). Low diastolic BP with active treatment was associated with increased risk of cardiovascular events, but only in patients with coronary heart disease at baseline ($P < .02$; hazard ratio for BP 65-60 mm Hg, 1.17; 95% confidence interval, 0.98-1.38). **CONCLUSIONS:** These findings support the hypothesis that antihypertensive treatment can be intensified to prevent cardiovascular events when systolic BP is not under control in older patients with systolic hypertension, at least until diastolic BP reaches 55 mm Hg. However, a prudent approach is warranted in patients with concomitant coronary heart disease, in whom diastolic BP should probably not be lowered to less than 70 mm Hg.

Hood SJ, Taylor KP, Ashby MJ, Brown MJ. The spironolactone, amiloride, losartan, and thiazide (SALT) double-blind crossover trial in patients with low-renin hypertension and elevated aldosterone-renin ratio. Circulation. 2007 Jul 17;116(3):268-75. Epub 2007 Jul 2.

BACKGROUND: There is continuing variation in diagnosis and estimated prevalence of primary hyperaldosteronism. The higher estimates encourage search for adrenal adenomas in patients with elevated ratios of plasma aldosterone to renin. However, it is more likely that patients with normal plasma K⁺ and aldosterone belong to the polygenic spectrum of low-renin hypertension rather than have the same monogenic syndrome as

classic Conn's. Our primary hypothesis was that in low-renin patients with normal plasma K⁺ and aldosterone, a thiazide diuretic, bendroflumethiazide, would be as effective as spironolactone in overcoming the Na⁺ retention and lowering blood pressure. Secondary objectives were to compare the dose response for each diuretic and to evaluate amiloride as an alternative to spironolactone. **METHODS AND RESULTS:** Fifty-seven patients entered and 51 patients completed a placebo-controlled, double-blind, randomized crossover trial. Entry criteria included low plasma renin, normal K⁺, elevated aldosterone-renin ratio, and a previous systolic blood pressure response to spironolactone of ≥ 20 mm Hg. Two doses each of spironolactone and bendroflumethiazide were compared. The crossover also included amiloride and losartan. Outcome measures were blood pressure, plasma renin, and other biochemical markers of diuretic action. Spironolactone 100 mg and bendroflumethiazide 5 mg caused similar falls in systolic blood pressure, whereas bendroflumethiazide 2.5 mg was 5/2 mm Hg less effective in reducing blood pressure than either bendroflumethiazide 5 mg or spironolactone 50 mg ($P < 0.005$). Amiloride 40 mg was as effective as the other diuretics. Biochemical indices of natriuresis showed bendroflumethiazide to be less effective than either spironolactone or amiloride; plasma renin rose 4-fold on spironolactone but only 2-fold on bendroflumethiazide ($P = 0.003$). **CONCLUSIONS:** In hypertensive patients with a low plasma renin but normal K⁺, bendroflumethiazide 5 mg was as effective as spironolactone 100 mg in lowering blood pressure, despite patients being selected for a previous large fall in blood pressure on spironolactone. Because this result differs from that expected in primary hyperaldosteronism, our finding argues against low-renin hypertension including a large, undiagnosed pool of primary hyperaldosteronism. However, spironolactone was the more effective natriuretic agent, suggesting that inappropriate aldosterone release or response may still contribute to the Na⁺ retention of low-renin hypertension.

Chapman N, Dobson J, Wilson S, Dahlöf B, Sever PS, Wedel H, Poulter NR; Anglo-Scandinavian Cardiac Outcomes Trial Investigators. Effect of spironolactone on blood pressure in subjects with resistant hypertension. *Hypertension.* 2007 Apr;49(4):839-45. Epub 2007 Feb 19.

Spironolactone is recommended as fourth-line therapy for essential hypertension despite few supporting data for this indication. We evaluated the effect among 1411 participants in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm who received spironolactone mainly as a fourth-line antihypertensive agent for uncontrolled blood pressure and who had valid BP measurements before and during spironolactone treatment. Among those who received spironolactone, the mean age was 63 years (SD: ± 8 years), 77% were men, and 40% had diabetes. Spironolactone was initiated a median of 3.2 years (interquartile range: 2.0 to 4.4 years) after randomization and added to a mean of 2.9 (SD: ± 0.9) other antihypertensive drugs. The median duration of spironolactone treatment was 1.3 years (interquartile range: 0.6 to 2.6 years). The median dose of spironolactone was 25 mg (interquartile range: 25 to 50 mg) at both the start and end of the observation period. During spironolactone therapy, mean blood pressure fell from 156.9/85.3 mm Hg (SD: $\pm 18.0/11.5$ mm Hg) by 21.9/9.5 mm Hg (95% CI: 20.8 to

0/9.0 to 10.1 mm Hg; $P < 0.001$); the BP reduction was largely unaffected by age, sex, smoking, and diabetic status. Spironolactone was generally well tolerated; 6% of participants discontinued the drug because of adverse effects. The most frequent adverse events were gynecomastia or breast discomfort and biochemical abnormalities (principally hyperkalemia), which were recorded as adverse events in 6% and 2% of participants, respectively. In conclusion, spironolactone effectively lowers blood pressure in patients with hypertension uncontrolled by a mean of approximately 3 other drugs. Although nonrandomized and not placebo controlled, these data support the use of spironolactone in uncontrolled hypertension.

Hiltunen TP, Suonsyrjä T, Hannila-Handelberg T, Paavonen KJ, Miettinen HE, Strandberg T, Tikkanen I, Tilvis R, Pentikäinen PJ, Virolainen J, Kontula K. Predictors of antihypertensive drug responses: initial data from a placebo-controlled, randomized, cross-over study with four antihypertensive drugs (The GENRES Study). Am J Hypertens. 2007 Mar;20(3):311-8.

BACKGROUND: Only a minority of hypertensive individuals is adequately controlled for their hypertension, partially because reliable predictors for efficient antihypertensive drug therapy are lacking. **METHODS:** In a prospective, randomized, double-blind, cross-over, placebo-controlled study (The GENRES Study), 208 moderately hypertensive Finnish men (aged 35 to 60 years) were treated for 4 weeks with antihypertensive drugs from four different classes: amlodipine (5 mg), bisoprolol (5 mg), hydrochlorothiazide (25 mg), or losartan (50 mg) daily. Each individual received each of the four monotherapies in a randomized order. Four-week placebo periods were included before and between drug treatment periods. Antihypertensive responses were assessed with 24-h ambulatory and office measurements and analyzed according to age, body mass index, triceps skin fold thickness, waist-to-hip ratio, duration of hypertension, number of previous antihypertensive drugs, number of affected parents, and blood pressure (BP) levels, and profiles during placebo periods. **RESULTS:** The median BP responses in 24-h ambulatory recordings (systolic/diastolic) were 11/8 mm Hg for bisoprolol, 9/6 mm Hg for losartan, 7/5 mm Hg for amlodipine, and 5/2 mm Hg for hydrochlorothiazide. The highest pairwise within-subject correlations in BP responses were seen for the combinations of bisoprolol-losartan and amlodipine-hydrochlorothiazide. The BP responses to bisoprolol and losartan did not vary according to the variables. Amlodipine and hydrochlorothiazide responses were positively correlated with age, placebo BP level, and lower night-time dipping on placebo. **CONCLUSIONS:** Baseline clinical and BP parameters may be used to predict the efficacy of antihypertensive therapies. The GENRES Study material should provide an excellent platform for future pharmacogenetic analyses of antihypertensive drug responsiveness.

Kintscher U, Bramlage P, Paar WD, Thoenes M, Unger T. Irbesartan for the treatment of hypertension in patients with the metabolic syndrome: a sub analysis of the Treat to Target post authorization survey. Prospective observational, two armed study in 14,200 patients. Cardiovasc Diabetol. 2007 Apr 3;6:12.

OBJECTIVES: The metabolic syndrome is a cluster of cardiovascular risk factors leading to an increased risk for the subsequent development of diabetes and cardiovascular morbidity and mortality. Blocking the renin-angiotensin system has been shown to prevent cardiovascular disease and delay the onset of diabetes. Irbesartan is an angiotensin receptor blocker (ARB) which has been shown to possess peroxisome proliferator-activated receptor gamma (PPAR γ) activating properties, and to have a favorable metabolic profile. Current discussion is whether the addition of small doses of hydrochlorothiazide changes this profile. Therefore the efficacy, safety and metabolic profile of Irbesartan either as monotherapy or in combination therapy was assessed in patients with the metabolic syndrome in a large observational cohort in primary care.

RESEARCH DESIGN AND METHODS: Multicenter, prospective, two-armed, post authorization study over 9 months in 14,200 patients with uncontrolled hypertension with and without the metabolic syndrome (doctors' diagnosis based on the Adult Treatment Panel III criteria 2001). Blood pressure was measured sphygmomanometrically and cardiovascular risk factors making up the criteria for the metabolic syndrome were assessed.

MAIN OUTCOME MEASURES: Systolic (SBP) and diastolic (DBP) blood pressure reduction, response, and normalization (systolic and diastolic), changes in fasting glucose, waist circumference (abdominal obesity), serum triglycerides and HDL cholesterol as well as the proportion of patients fulfilling the criteria for the metabolic syndrome. Number and nature of adverse events (AEs).

RESULTS: After 9 month the use of Irbesartan in monotherapy resulted in a significant reduction of blood pressure (SBP: -26.3 +/- 10.1 mmHg/DBP-13.0 +/- 6.6 mmHg, both $p < 0.0001$) in patients with the metabolic syndrome. This was accompanied by a reduction in cardiovascular risk factors: HDL cholesterol (+3.6 +/- 7.2 mg/dl in men, +3.8 +/- 6.5 mg/dl in women, both $p < 0.0001$), serum triglycerides (-28.6 +/- 52.1 mg/dl, $p < 0.0001$), fasting blood glucose (-8.4 +/- 25.1 mg/dl, $p < 0.0001$) and waist circumference (-2.4 +/- 11.9 cm in men, -1.2 +/- 14.2 in women, both $p < 0.0001$) were significantly improved. Irbesartan combination therapy (12.5 mg HCTZ) in patients with the metabolic syndrome: blood pressure reduction (SBP: -27.5 +/- 10.1 mmHg/DBP: -14.1 +/- 6.6 mmHg, both $p < 0.0001$), improvement in HDL cholesterol (+4.0 +/- 6.8 mg/dl in men, +3.4 +/- 6.8 in women, both $p < 0.0001$), triglycerides (-34.1 +/- 52.6 mg/dl, $p < 0.0001$), fasting blood glucose (-10.0 +/- 24.7, $p < 0.0001$) and waist circumference (-3.2 +/- 12.7 cm in men, -1.7 +/- 14.4 in women, both $p < 0.0001$). Tolerability was excellent: only 0.6% of patients experienced an AE.

CONCLUSION: There was a significant improvement in blood pressure and metabolic risk factors as a result of Irbesartan treatment. There was no evidence of a difference between monotherapy and combination therapy with regard to the cardiovascular risk profile.

Oparil S, Yarows SA, Patel S, Fang H, Zhang J, Satlin A. Efficacy and safety of combined use of aliskiren and valsartan in patients with hypertension: a randomised, double-blind trial. Lancet. 2007 Jul 21;370(9583):221-9.

BACKGROUND: The aim of this study was to assess dual renin system intervention with the maximum recommended doses of aliskiren and valsartan, compared with each

drug alone in patients with hypertension. **METHODS:** In this double-blind study, 1797 patients with hypertension (mean sitting diastolic blood pressure 95-109 mm Hg and 8-h daytime ambulatory diastolic blood pressure \geq 90 mm Hg) were randomly assigned to receive once-daily aliskiren 150 mg (n=437), valsartan 160 mg (455), a combination of aliskiren 150 mg and valsartan 160 mg (446), or placebo (459) for 4 weeks, followed by forced titration to double the dose to the maximum recommended dose for another 4 weeks. The primary endpoint was change in mean sitting diastolic blood pressure from baseline to week 8 endpoint. Analyses were done by intention to treat. This trial is registered at ClinicalTrials.gov with the number NCT00219180. **FINDINGS:** 196 (11%) patients discontinued study treatment before the end of the trial (63 in the placebo group, 53 in the aliskiren group, 43 in the valsartan group, and 37 in the aliskiren/valsartan group), mainly due to lack of therapeutic effect. At week 8 endpoint, the combination of aliskiren 300 mg and valsartan 320 mg lowered mean sitting diastolic blood pressure from baseline by 12.2 mm Hg, significantly more than either monotherapy (aliskiren 300 mg 9.0 mm Hg decrease, $p < 0.0001$; valsartan 320 mg, 9.7 mm Hg decrease, $p < 0.0001$), or with placebo (4.1 mm Hg decrease, $p < 0.0001$). Rates of adverse events and laboratory abnormalities were similar in all groups. **INTERPRETATION:** The combination of aliskiren and valsartan at maximum recommended doses provides significantly greater reductions in blood pressure than does monotherapy with either agent in patients with hypertension, with a tolerability profile similar to that with aliskiren and valsartan alone.

Oh BH, Mitchell J, Herron JR, Chung J, Khan M, Keefe DL. Aliskiren, an oral renin inhibitor, provides dose-dependent efficacy and sustained 24-hour blood pressure control in patients with hypertension. J Am Coll Cardiol. 2007 Mar 20;49(11):1157-63

OBJECTIVES: This dose-ranging study evaluated the antihypertensive efficacy and tolerability of aliskiren in patients with mild-to-moderate hypertension.

BACKGROUND: Low blood pressure (BP) control rates among patients with hypertension indicate a need for improved treatment options. This study investigates aliskiren, the first in a new antihypertensive class called renin inhibitors. **METHODS:** Patients with mean sitting diastolic BP 95 to 109 mm Hg were randomized to aliskiren 150, 300, or 600 mg or placebo once daily for 8 weeks. Patients completing this treatment phase entered a 2-week treatment-free withdrawal period. Office BP was recorded at baseline, weeks 2, 4, 6, and 8 of treatment, and 4 days and 2 weeks after cessation of treatment. A subgroup of patients underwent ambulatory BP monitoring. **RESULTS:** In total, 672 patients were randomized to treatment. After 8 weeks, aliskiren 150, 300, and 600 mg significantly reduced mean sitting BP (systolic/diastolic) by 13.0/10.3, 14.7/11.1, and 15.8/12.5 mm Hg, respectively, versus 3.8/4.9 mm Hg with placebo (all $p < 0.0001$ for systolic and diastolic BP). The BP-lowering effect of aliskiren persisted for up to 2 weeks after treatment withdrawal. Aliskiren significantly reduced mean 24-h ambulatory BP ($p < 0.0001$ vs. placebo with all doses) exhibiting smooth, sustained effects and high trough-to-peak ratios. Aliskiren was well tolerated; overall adverse event rates were 40.1%, 46.7%, and 52.4% with aliskiren 150, 300, and 600 mg, respectively, and 43.0% with placebo. Few patients discontinued treatment due to adverse events.

CONCLUSIONS: Aliskiren provides significant antihypertensive efficacy in patients with hypertension, with no rebound effects on blood pressure after treatment withdrawal.

O'Brien E, Barton J, Nussberger J, Mulcahy D, Jensen C, Dicker P, Stanton A. Aliskiren reduces blood pressure and suppresses plasma renin activity in combination with a thiazide diuretic, an angiotensin-converting enzyme inhibitor, or an angiotensin receptor blocker. Hypertension. 2007 Feb;49(2):276-84. Epub 2006 Dec 11.

Thiazide diuretics, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers all cause reactive rises in plasma renin activity. We hypothesized that renin inhibition with aliskiren would prevent this reactive rise and also enhance blood pressure lowering. In 3 open-label studies in which blood pressure was assessed with ambulatory measurement, aliskiren was administered to patients with mild-to-moderate hypertension in combination with hydrochlorothiazide (n=23), ramipril (n=21), or irbesartan (n=23). In the diuretic combination study, the addition of 25 mg of hydrochlorothiazide to 150 mg of aliskiren daily for 3 weeks significantly lowered daytime pressure, compared with aliskiren monotherapy (systolic/diastolic mean change from baseline [SEM]: daytime: -18.4 [2.1]/ -10.6 [1.7] versus -10.4 [1.8]/-5.8 [1.4]; nighttime: -15.6 [2.7]/-8.1 [1.8] versus -8.8 [2.9]/-5.0 [2.2]). In the angiotensin-converting enzyme inhibitor combination study, the addition of 75 or 150 mg of aliskiren to 5 mg of ramipril alone for 3 weeks further lowered both daytime and nighttime pressures compared with ramipril monotherapy (daytime: -10.5 [2.9]/-8.1 [2.1] and -14 [3.7]/-8.7 [2.3] versus -6.1 [2.4]/-5.9 [1.5]; nighttime: -8.1 [2.6]/-5.3 [2.4] and -9.6 [3.4]/-5.3 [2.4] versus -2 [2.3]/-0.7 [2.2]). In the angiotensin receptor blocker combination study, the addition of 75 or 150 mg of aliskiren to 150 mg of irbesartan alone, for 3 weeks, resulted in significantly lower nighttime pressures compared with irbesartan monotherapy (daytime: -14.8 [2]/-8.2 [1.3] and -13.3 [1.6]/-6.8 [0.9] versus -11.4 [1.6]/-6.5 [1.1]; nighttime: -16.1 [2.4]/-8.6 [1.7] and -13.2 [2.7]/-7.2 [1.9] versus -9.0 [2.5]/-4.7 [1.9]). Aliskiren (150 mg) alone significantly inhibited plasma renin activity by 65% (P<0.0001). Ramipril and irbesartan monotherapy caused 90% and 175% increases in plasma renin activity, respectively. By contrast, when aliskiren was coadministered with hydrochlorothiazide, ramipril, or irbesartan, plasma renin activity did not increase but remained similar to baseline levels or was decreased (combination therapy versus untreated; median [interquartile range]; aliskiren and hydrochlorothiazide: 0.4 [0.2 to 1.1] versus 0.7 [0.5 to 1.3]; ramipril and aliskiren: 0.5 [0.3 to 0.9] versus 0.6 [0.5 to 0.8]; irbesartan and aliskiren: 0.4 [0.2 to 0.9] versus 0.6 [0.4 to 0.9]). These results suggest that renin inhibition with aliskiren in these combinations increases renin-angiotensin system suppression, improves 24-hour blood pressure control, and may ultimately provide better end-organ protection in patients with hypertension.

THEME E: Antihypertensive Therapies for Something Other than Hypertension

Solomon SD, Janardhanan R, Verma A, Bourgoun M, Daley WL, Purkayastha D, Lacourcière Y, Hippler SE, Fields H, Naqvi TZ, Mulvagh SL, Arnold JM, Thomas JD, Zile MR, Aurigemma GP; Valsartan In Diastolic Dysfunction (VALIDD) Investigators. Effect of angiotensin receptor blockade and antihypertensive drugs on diastolic function

in patients with hypertension and diastolic dysfunction: a randomised trial. Lancet. 2007 Jun 23;369(9579):2079-87.

BACKGROUND: Diastolic dysfunction might represent an important pathophysiological intermediate between hypertension and heart failure. Our aim was to determine whether inhibitors of the renin-angiotensin-aldosterone system, which can reduce ventricular hypertrophy and myocardial fibrosis, can improve diastolic function to a greater extent than can other antihypertensive agents. **METHODS:** Patients with hypertension and evidence of diastolic dysfunction were randomly assigned to receive either the angiotensin receptor blocker valsartan (titrated to 320 mg once daily) or matched placebo. Patients in both groups also received concomitant antihypertensive agents that did not inhibit the renin-angiotensin system to reach targets of under 135 mm Hg systolic blood pressure and under 80 mm Hg diastolic blood pressure. The primary endpoint was change in diastolic relaxation velocity between baseline and 38 weeks as determined by tissue doppler imaging. Analyses were done by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00170924. **FINDINGS:** 186 patients were randomly assigned to receive valsartan; 198 were randomly assigned to receive placebo. 43 patients were lost to follow-up or discontinued the assigned intervention. Over 38 weeks, there was a 12.8 (SD 17.2)/7.1 (9.9) mm Hg reduction in blood pressure in the valsartan group and a 9.7 (17.0)/5.5 (10.2) mm Hg reduction in the placebo group. The difference in blood pressure reduction between the two groups was not significant. Diastolic relaxation velocity increased by 0.60 (SD 1.4) cm/s from baseline in the valsartan group ($p < 0.0001$) and 0.44 (1.4) cm/s from baseline in the placebo group ($p < 0.0001$) by week 38. However, there was no significant difference in the change in diastolic relaxation velocity between the groups ($p = 0.29$). **INTERPRETATION:** Lowering blood pressure improves diastolic function irrespective of the type of antihypertensive agent used.

Phillips CO, Kashani A, Ko DK, Francis G, Krumholz HM. Adverse effects of combination angiotensin II receptor blockers plus angiotensin-converting enzyme inhibitors for left ventricular dysfunction: a quantitative review of data from randomized clinical trials. Arch Intern Med. 2007 Oct 8; 167(18):1930-6.

BACKGROUND: We performed a meta-analysis of randomized controlled trials to assess ongoing concerns about the safety profile of combination angiotensin II receptor blockers (ARBs) plus angiotensin-converting enzyme (ACE) inhibitors in symptomatic left ventricular dysfunction. **METHODS:** MEDLINE (January 1966-December 2006) and Web sites for the National Institute of Health Clinical Trials and the Food and Drug Administration were searched for eligible RCTs that included 500 or more subjects, had a follow-up of 3 months or longer, and reported adverse effects. We used a random effects model to calculate the relative risk (RR) and 95% confidence interval (CI) for the following outcome measures: medication discontinuations because of adverse effects, worsening renal function (an increase in serum creatinine level of > 0.5 mg/dL [to convert to micromoles per liter, multiply by 88.4]), hyperkalemia (serum potassium level > 5.5 mEq/L [to convert to millimoles per liter, multiply by 1]), and symptomatic hypotension. **RESULTS:** Four studies ($N = 17\ 337$; mean follow-up, 25 months [range,

11-41 months]) were selected. Combination ARB plus ACE inhibitor vs control treatment that included ACE inhibitors was associated with significant increases in medication discontinuations because of adverse effects in patients with chronic heart failure (RR, 1.38 [95% CI, 1.22-1.55]) or in patients with acute myocardial infarction with symptomatic left ventricular dysfunction (RR, 1.17 [95% CI, 1.03-1.34]), and for both conditions there were significant increases in worsening renal function (RR, 2.17 [95% CI, 1.59-2.97] and RR, 1.61 [95% CI, 1.31-1.98], respectively), hyperkalemia (RR, 4.87 [95% CI, 2.39-9.94] and RR, 1.33 [95% CI, 0.90-1.98], respectively; the latter was not significant), and symptomatic hypotension (RR, 1.50 [95% CI, 1.09-2.07], and RR, 1.48 [95% CI, 1.33-3.18], respectively). CONCLUSION: Combination ARB plus ACE inhibitor therapy in subjects with symptomatic left ventricular dysfunction was accompanied by marked increases in adverse effects.

Shlyakhto E. *Observational Study on Cognitive function And Systolic blood pressure Reduction (OSCAR): preliminary analysis of 6-month data from > 10,000 patients and review of the literature.* Curr Med Res Opin. 2007 Nov;23 Suppl 5:S13-8.

Given the ageing population, dementia is an ever-increasing health burden. A positive correlation between cognitive decline or dementia and blood pressure levels has been indicated. There is, however, conflicting evidence over the definitive link between the use of antihypertensives and the subsequent reduction of cognitive decline. The specific use of angiotensin II receptor blockers (ARBs) in preventing vascular dementia has been investigated with eprosartan treatment. In animal studies utilising stroke-prone rats, eprosartan has been shown to reduce end-organ damage of the heart and kidneys in a study assessing cardiomyopathy and renal failure. The Morbidity and mortality after Stroke, Eprosartan compared with nitrendipine for Secondary prevention (MOSES) study, assessing 1405 patients, has shown the cerebroprotective effects of eprosartan compared with the calcium channel blocker nitrendipine. In this study, however, no change in cognitive function, as assessed by the mini-mental status examination (MMSE) score, was seen between the treatment groups. The Observational Study on Cognitive function And systolic blood pressure Reduction (OSCAR) trial, including more than 60,000 hypertensive patients, also assessed the ability of eprosartan to alter the MMSE score. In contrast to the MOSES trial, preliminary data from 10,000 patients after 6 months of treatment identified a decrease in blood pressure alongside a significant increase in MMSE score. Specific subpopulations within this study, including the elderly, patients with higher initial systolic blood pressure and patients with a body mass index (BMI) of 25-30 kg/m² showed the greatest change in MMSE score. These data indicate an association with blood pressure reduction and improvement of cognitive function with eprosartan treatment.

Ichikawa Y *Comparative effects of telmisartan and valsartan on insulin resistance in hypertensive patients with metabolic syndrome.* Intern Med. 2007;46(17):1331-6. Epub 2007 Sep 3.

OBJECTIVE: Metabolic syndrome (MetS) is a cluster of metabolic abnormalities that

includes hyperglycemia, dyslipidemia, hypertension and increased waist circumference. Individuals with this syndrome are at increased risk for development of cardiovascular disease. Since an insulin-resistance state has a critical role in the development of MetS, there is growing concern about insulin-sensitizing effects of antihypertensives, including angiotensin II receptor blockers (ARBs). Telmisartan has been reported to have an effect on the activity of peroxisome proliferator-activated receptor gamma, a well-known target for insulin-sensitizing antidiabetic drugs. The aim of this study was to determine the effects of administration of two different ARBs at low doses (telmisartan at 20 mg/day and valsartan at 40 mg/day) on insulin sensitivity. **METHODS:** Patients with MetS meeting the Japanese criteria were treated with telmisartan or valsartan for 4 weeks in combination with lifestyle modification. **RESULTS:** A significant reduction in blood pressure was found after 4 weeks of both treatments. The homeostasis model assessment of insulin resistance (HOMA-R) was significantly reduced by telmisartan compared to the baseline value (3.11 ± 2.06 vs 2.56 ± 1.48 , $p=0.031$) but was not significantly changed by valsartan. A statistically significant correlation was found between HOMA-R at baseline and changes in HOMA-R after 4 weeks of treatment only in telmisartan-treated subjects. Body mass index, glycosylated hemoglobin and lipid profile were not changed by either treatment. **CONCLUSION:** Our data revealed that treatment with telmisartan even at a low dose improves insulin sensitivity in hypertensive patients with MetS. This ameliorating effect of telmisartan on glucose metabolism clinically deserves to be considered.