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# Key Articles and Guidelines in the Management of Hypertension: 2008 Update

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## Abstract and Introduction

### Abstract

Hypertension remains a major risk factor for cardiovascular disease. The optimal choice of pharmacologic and nonpharmacologic treatment regimens is based on a plethora of published literature. This compilation is the initial update to the Key Articles and Guidelines in the Management of Hypertension authored by members of the Cardiology Practice and Research Network of the American College of Clinical Pharmacy, which appeared in Pharmacotherapy in 2004. We present synopses of clinical trials, meta-analyses, clinical practice guidelines, and other pertinent literature published between May 2003 and June 2007.

### Introduction

This compilation updates part of a series of annotated bibliographies compiled by members of the Cardiology Practice and Research Network of the American College of Clinical Pharmacy regarding acute coronary syndromes,<sup>[1]</sup> arrhythmias,<sup>[2]</sup> dyslipidemias,<sup>[3]</sup> systolic heart failure,<sup>[4]</sup> and hypertension.<sup>[5]</sup> In addition, annotated bibliographies for cardiac transplantation, genomics, and venous thromboembolism are being developed. The current panel of seven authors and reviewers identified key articles published since the previous bibliography appeared in 2004 that have

substantially affected our understanding and management of hypertension. We include primary literature, pertinent review articles, and clinical practice guidelines.

## Major Clinical Trials

**Nissen SE, Tuzcu EM, Libby P, et al, for the CAMELOT Investigators.** Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study -- a randomized controlled trial. *JAMA* 2004;292:2217-25.

The Comparison of Amlodipine versus Enalapril to Limit Occurrences of Thrombosis (CAMELOT) study was designed to test whether reducing blood pressure with amlodipine (target dose 10 mg/day) or enalapril (target dose 20 mg/day) for 24 months improves the risk of cardiovascular death, nonfatal myocardial infarction, resuscitated cardiac arrest, coronary revascularization, hospitalization for angina, hospitalization for heart failure, fatal or nonfatal stroke or transient ischemic attack, and newly diagnosed peripheral vascular disease. For this double-blind, multicenter, randomized placebocontrolled trial, researchers enrolled 1991 patients with coronary artery disease (CAD) and a baseline diastolic blood pressure less than 100 mm Hg (mean baseline blood pressure 129/78 mm Hg). Blood pressure increased by 0.7/0.6 mm Hg in the placebo group and decreased by 4.8/2.5 and 4.9/2.4 mm Hg in amlodipine and enalapril groups, respectively (both  $p < 0.001$  vs placebo group). The rate of cardiovascular events was lower in patients receiving amlodipine (16.6%,  $p = 0.003$ ) or enalapril (20.2%,  $p = 0.16$ ) than in patients receiving placebo (23.1%). A nonsignificant trend suggested the superiority of amlodipine compared with enalapril in the primary end point of adverse cardiovascular events ( $p = 0.1$ ). The benefits of amlodipine were mainly driven by a reduction in the risk of hospitalization for angina and revascularization. Therefore, results of the CAMELOT study suggest that the addition of enalapril or amlodipine may be beneficial in patients with stable CAD and normal blood pressure.

**Julius S, Kjeldsen SE, Weber M, et al, for the VALUE Trial Group.** Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet* 2004;363: 2022-31.

The Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) was designed to determine whether valsartan 80-160 mg/day was superior to amlodipine 5-10 mg/day for achieving a blood pressure less than 140/90 mm Hg. At the investigators' discretion, hydrochlorothiazide 12.5-25 mg/day, followed by other antihypertensive drugs, could be added to reach the target. This multicenter, double-blind, randomized trial included 15,245 patients aged 50 years or older who were at high risk of having a cardiovascular event. The primary end point was cardiac morbidity and mortality; the latter was defined as sudden cardiac death, fatal myocardial infarction, death during or after percutaneous coronary intervention or coronary artery bypass grafting, death due to heart failure, as well as death associated with recent myocardial infarction on autopsy, heart failure requiring hospital management, nonfatal myocardial infarction, or emergency procedures to prevent myocardial infarction. After a mean follow-up of 4.2 years, the primary end point did not significantly differ between the valsartan and amlodipine groups (10.6% and 10.4%, respectively,  $p = 0.49$ ); however, blood pressure reduction was more pronounced with amlodipine, particularly in the first 6 months (by 4.0/2.1 mm Hg at 1 mo and 2.1/1.6 mm Hg at 6 mo). During this time, fewer events occurred in the

amlodipine group than in the valsartan group. However, use of a relatively low dose of valsartan 160 mg/day possibly confounded this result. These differences in blood pressure control considerably restricted the scope of conclusions regarding the possible superiority of valsartan for a similar reduction in blood pressure. Still, the authors emphasized that hypertension should be aggressively treated over weeks, not months or years, in high-risk patients.

**Lithell H, Hansson L, Skoog I, et al, for the SCOPE Study Group.** The study on cognition and prognosis in the elderly (SCOPE): principal results of a randomized double-blind intervention trial. *J Hypertens* 2003;21:875-86.

The SCOPE trial was a multicenter trial of 4964 patients aged 70-89 years (mean 76.4 yrs) who had untreated or treated hypertension with a systolic blood pressure of 160-179 mm Hg and/or a diastolic blood pressure of 90-99 mm Hg. Patients were randomized to receive candesartan 8-16 mg/day or placebo. Before randomization, any previous antihypertensive agent was standardized to hydrochlorothiazide 12.5 mg/day. After the initiation of the study drug, the investigators recommended doubling the dose of the study drug (from 8 to 16 mg for candesartan or matching placebo) if the patient's systolic or diastolic pressure was above 160 or 85 mm Hg, respectively, or if the systolic pressure was reduced by less than 10 mm Hg at any consecutive visit. Open-label antihypertensive agents were then added, as needed, if the systolic or diastolic pressure remained at or above 160 or 90 mm Hg, respectively. The primary outcome was cardiovascular mortality, nonfatal myocardial infarction, or nonfatal stroke. Although reductions in blood pressure were significantly greater in the candesartan group (21.7/10.8 mm Hg) than in the control group (18.5/9.2 mm Hg,  $p < 0.001$ ), no significant reduction in the primary end point was observed after a mean follow-up of 44.6 months. The investigators observed no benefit in the risk of dementia or in cognitive function (evaluated by using the Mini-Mental State Examination). Therefore, results of the SCOPE study suggest that candesartan is not superior to conventional treatment in elderly patients with hypertension.

**Shrader J, Lüders S, Kulschewski A, et al, for MOSES Study Group.** Morbidity and mortality after stroke, eprosartan compared with nitrendipine for secondary prevention: principal results of a prospective randomized controlled study (MOSES). *Stroke* 2005;36:1218-26.

The purpose of the Morbidity and Mortality after Stroke, Eprosartan Compared with Nitrendipine for Secondary Prevention (MOSES) trial was to test the hypothesis that eprosartan (starting dose 600 mg/day) is superior to nitrendipine (starting dose 10 mg/day) in reducing the combined end point of all-cause mortality and nonfatal cerebrovascular and cardiovascular events in hypertensive patients who had experienced a cerebrovascular event in the last 24 months. Nonfatal events encompassed intracerebral hemorrhage, stroke, transient ischemic attack and/or a prolonged and reversible ischemic neurologic deficit, or any cardiovascular event. Of 1405 patients included in this open-label study with blinded end points, 1352 were eligible for analysis; this number was slightly lower than the predefined goal of 1600 patients to achieve adequate power. At their discretion, investigators could increase the dosage of the study drug or add a nonstudy antihypertensive agent to reach the target blood pressure of less than 140/90 mm Hg. Of note, the mean time after the qualifying cerebral event was almost 1 year, and only 3% of patients were enrolled within 1 week of the event. Hence, the results of this study do not apply to patients with an acute stroke. Blood pressure control was similar in both groups. After a mean follow-up of 2.5 years, eprosartan significantly reduced the total number

of events compared with nitrendipine (206 vs 255,  $p=0.014$ ). Eprosartan appeared to be superior to nitrendipine in reducing the total number of both cerebrovascular ( $p=0.03$ ) and cardiovascular ( $p=0.06$ ) events, although the difference in the latter was not statistically significant. In terms of the time to the first event, the benefit of eprosartan was still apparent with cardiovascular ( $p=0.03$ ) but not cerebrovascular ( $p=0.43$ ) events. No significant differences were observed in mortality or in improved functional or cognitive parameters. The MOSES data suggest that eprosartan is superior to nitrendipine. However, noteworthy limitations, such as the open design, the limited number of patients, and the fact that the primary analysis was based on the total number of events rather than traditional survival, make the results far from definitive.

**Julius S, Nesbitt SD, Egan BM, et al, for the Trial of Preventing Hypertension (TROPHY) Study Investigators.** Feasibility of treating prehypertension with an angiotensin-receptor blocker. *N Engl J Med* 2006;354:1685–97.

The Trial of Preventing Hypertension (TROPHY) was the first large, multicenter, randomized trial designed to investigate the feasibility of treating prehypertension (defined as repeated measurements of  $130\text{--}139/\leq 89$  or  $\leq 139/85\text{--}89$  mm Hg). For 2 years, 809 patients received candesartan 16 mg/day or placebo, then all patients received placebo for 2 years. Mean follow-up was 3.56 years. After the randomized phase, 13.6% of patients in the candesartan group and 40.4% in the placebo group developed hypertension ( $p<0.001$ ). After the all-placebo phase, these rates increased to 53.2% and 63.0% in the candesartan and placebo groups, respectively, ( $p=0.007$ ). Hence, hypertension prevention was greatly reduced when candesartan was stopped. The hypotensive effect of candesartan may have masked overt hypertension rather than modify the course of disease. One major limitation was that the definition of new-onset hypertension consisted of the following four possibilities: systolic pressure 140 mm Hg or higher and/or diastolic pressure 90 mm Hg or higher on three study visits, systolic pressure 160 mm Hg or higher and/or diastolic pressure 100 mm Hg or higher on one visit, blood pressure requiring pharmacotherapy, or systolic pressure 140 mm Hg or higher and/or diastolic pressure 90 mm Hg or higher at the 48-month visit. According to the study design, patients receiving candesartan were unlikely to meet the first definition in the first half of the study as they were unlikely to have blood pressures of 140/90 mm Hg or higher while receiving study drug. Of importance, candesartan reduced hypertension only according to this part of the definition and not according to the other three. Given that nearly two thirds of patients developed hypertension during the study and that treating prehypertension may or may not improve clinical outcomes or be costeffective, pharmacologic treatment is not recommended for patients with prehypertension unless they have diabetes mellitus, renal dysfunction, established cardiovascular disease, or a high risk for cardiovascular disease. However, all individuals with prehypertension should be counseled to implement lifestyle modifications.

**Ruggenti P, Fassi A, Ilieva AP, et al, for the Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) Investigators.** Preventing microalbuminuria in type 2 diabetes. *N Engl J Med* 2004;351:1941–51.

The Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) was a multicenter, double-blind, randomized study designed to compare trandolapril and/or verapamil with placebo for preventing microalbuminuria in 1024 patients with hypertension, type 2 diabetes, and normal urinary

albumin excretion. Patients received one of the following regimens: trandolapril 2 mg/day plus verapamil 180 mg/day, trandolapril 2 mg/day, verapamil 240 mg/day, or placebo. Other antihypertensive agents could be added to reach the target blood pressure of 120/80 mm Hg. After a median follow-up of 3.6 years, the frequency of microalbuminuria was reduced in patients receiving trandolapril alone (6.0%;  $p=0.01$  vs placebo,  $p=0.04$  vs verapamil alone) and trandolapril plus verapamil (5.7%;  $p=0.01$  vs placebo,  $p=0.02$  vs verapamil alone) compared with placebo (10%) or verapamil alone (11.9%,  $p=0.54$  vs placebo). Hence, treatment with trandolapril reduced the frequency of microalbuminuria in patients with type 2 diabetes and normal urinary albumin excretion. Verapamil had no impact on the risk of developing microalbuminuria when it was added to trandolapril or given alone compared with placebo.

**Appel LJ, Sacks FM, Carey VJ, et al, for the OmniHeart Collaborative Research Group.** Effects of protein, monounsaturated fat, and carbohydrate intake on blood pressure and serum lipids: results of the Omniheart randomized trial. *JAMA* 2005;294:2455–64.

Reduced intake of saturated fat is recommended to lower the risk of cardiovascular disease, yet the best macronutrient for replacement is unclear. The OmniHeart trial was designed as a prospective, three-period, crossover study to compare the effects of three diets low in saturated fat on blood pressure and low-density lipoprotein cholesterol. Patients weighed less than 350 lb and had prehypertension or stage 1 hypertension (blood pressure 120–159/80–99 mm Hg), a low-density lipoprotein cholesterol level below 220 mg/dl, and a triglyceride level below 750 mg/dl. Patients taking any drug that affected blood pressure or cholesterol level were excluded. Patients were randomized to a sequence of the three diets (carbohydrate, protein, or unsaturated fat), where each diet, or feeding period, lasted 6 weeks. A total of 159 patients completed all three feeding periods; 164 completed two. Each diet lowered systolic and diastolic blood pressures and low-density lipoprotein cholesterol values compared with baseline. High-density lipoprotein cholesterol values decreased with the carbohydrate and protein diets but were unchanged with the unsaturated fat diet. Triglyceride concentrations were lowered with the protein and unsaturated fat diets but unchanged with the carbohydrate diet. The three diets varied in terms of individual components of blood pressure and lipids, but none of the diets had an adverse effect. The authors concluded that adhering to recommended levels of saturated fat, cholesterol, fiber, fruit, vegetable, and mineral intake can improve cardiovascular risk factors.

**Bobrie G, Chatellier G, Genes N, et al.** Cardiovascular prognosis of "masked hypertension" detected by blood pressure selfmeasurement in elderly treated hypertensive patients. *JAMA* 2004;291:1342–9.

Blood pressure measurement with a mercury sphygmomanometer has been used to demonstrate the relationship between blood pressure and cardiovascular risk. However, limitations of this method include intraobserver variability, an inability to identify white-coat hypertension (i.e., hypertension observed in clinical settings but not at home), and environmentally toxic effects of mercury. In a prospective cohort study, investigators compared the prognostic value of home blood pressure monitoring with office measurement by general practitioners in 4939 patients over a mean of 3.2 years. After adjusting for traditional cardiovascular risk factors, the investigators found no significant difference in the primary end point of cardiovascular mortality. However, home systolic and diastolic blood pressures were predictive of cardiovascular events, both fatal (hazard ratio (HR) 1.02, 95%

confidence interval [CI] 1.01–1.02,  $p < 0.001$ ) and nonfatal (HR 1.02, 95% CI 1.01–1.03,  $p < 0.001$ ). Neither systolic nor diastolic pressures assessed in the office had significant prognostic value. With home measurement, the risk of cardiovascular events rose by 17.2% for each 10-mm Hg increase in systolic pressure and by 11.7% for each 5-mm Hg increase in diastolic pressure. The authors noted that the difference may have been related to reductions in inpatient variability, as the mean number of measurements was 27 at home versus six in the office. This study demonstrated the superior prognostic value of home versus office measurement of blood pressure. However, whether therapeutic decisions based on home monitoring provide any advantage over the current practice of office-based measurements is unknown.

**Ernst ME, Carter BL, Goerdts CJ, et al.** Comparative effects of hydrochlorothiazide and chlorthalidone on ambulatory and office blood pressure. *Hypertension* 2006;47:352–8.

Thiazide-like diuretics reduce stroke and cardiovascular events and are recommended by the Seventh Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) as the foundation for many antihypertensive drug regimens. Chlorthalidone was the antihypertensive studied in the landmark Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), the results of which are often extrapolated to hydrochlorothiazide. This randomized, single-blind, 8-week, active-treatment study was designed to assess changes in 24-hour mean systolic and diastolic ambulatory blood pressures between chlorthalidone and hydrochlorothiazide. Its initial crossover design was changed to a parallel arrangement because of a significant order-drug-time interaction. In the parallel design, chlorthalidone 25 mg/day reduced mean 24-hour systolic blood pressures more than hydrochlorothiazide 50 mg/day did, but the reduction was not statistically significant ( $p = 0.054$ ). The main reason was because chlorthalidone reduced nighttime systolic blood pressure significantly more than hydrochlorothiazide (mean  $\pm$  SD reductions of  $13.5 \pm 1.9$  vs  $6.4 \pm 1.7$  mm Hg in 30 patients in the crossover,  $p = 0.009$ ). No significant differences were observed in mean daytime systolic pressures or any diastolic pressures between the groups. Chlorthalidone and hydrochlorothiazide did not significantly differ in their effects on potassium concentration. The authors concluded that hydrochlorothiazide and chlorthalidone may not be interchangeable. Furthermore, the difference in efficacy manifested during nighttime hours, when it would have been overlooked if traditional daytime blood pressures were measured in the office. Future studies are needed to determine if these blood pressure differences are clinically meaningful.

**Bakris GL, Fonseca V, Katholi RE, et al, for the Gemini Investigators.** Metabolic effects of carvedilol versus metoprolol in patients with type 2 diabetes and hypertension: a randomized controlled trial. *JAMA* 2004;292:2227–36.

The relationship between glycemic control and cardiovascular events is well documented; however, only 37% of adults with diabetes achieve hemoglobin A1c goals. In addition, blood pressure goals are lower in patients with diabetes than in others, and multiple agents are required to achieve the targets. Guidelines recommend  $\beta$ -blockers as one of the agents to control blood pressure despite evidence for worsening glycemic control with this class of antihypertensives. Conversely, agents that block the renin-angiotensin system (RAS) not only lower blood pressure but also improve glycemic control. A prospective, randomized, parallel-group, multicenter analysis, Glycemic Effects in Diabetes

**Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives (GEMINI)**, was conducted to compare the effects of carvedilol and metoprolol tartrate on glycemic control in 1111 patients with hypertension and type 2 diabetes who were receiving a RAS blocker. After 5 months, hemoglobin A<sub>1c</sub> values (primary outcome) were significantly higher with metoprolol than with carvedilol (mean difference from baseline 0.13%, 95% CI -0.22% to -0.04%, p=0.004). Carvedilol and metoprolol also significantly differed in prespecified secondary outcomes. Patients taking metoprolol gained more weight (mean difference from baseline +1.2% vs +0.17%, p<0.001) and had higher total cholesterol levels (-0.4% vs -3.3%, p=0.001), triglyceride levels (+13.2% vs +2.2%, p<0.001), and insulin resistance (-2.0% vs -9.1%, p=0.004) than those taking carvedilol. The authors concluded that, in the presence of RAS blockade,  $\beta$ -blockers are well tolerated and effective for achieving blood pressure targets and that blood glucose effects are more favorable with carvedilol than with metoprolol.

**Bakris GL, Weir MR, Shanifar S, et al, for the RENAAL Study Group.** Effects of blood pressure level on progression of diabetic nephropathy: results from the RENAAL study. *Arch Intern Med* 2003;163:1555–65.

The Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study was originally reported in 2001. In this post hoc analysis, investigators compared resulting blood pressures and outcomes to characterize the role of blood pressure and different antihypertensive agents in predicting progression to end-stage renal disease (ESRD). After following 1513 patients with type 2 diabetes and nephropathy for a mean of 3.4 years, they found that compared with placebo, significantly fewer patients in the losartan group had doubling of serum creatinine concentrations, ESRD, or death (composite primary end point). The risk of ESRD increased in an independent linear fashion when baseline systolic blood pressures were above 130 mm Hg. Likewise, the risk of developing the primary outcome, including ESRD alone, was significantly higher in patients with baseline pulse pressures above 70 mm Hg than in patients with pulse pressures below 60 mm Hg. Diastolic blood pressures did not have such predictive ability. When effects of specific classes of baseline antihypertensives were examined, dihydropyridine calcium channel blockers (CCBs) increased the risk of reaching the primary end point compared with an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB). Losartan and dihydropyridine CCBs lowered the risk of renal outcomes compared with placebo. The authors concluded that these results support the importance of lowering blood pressure to goal to prevent the progression of nephropathy and the possible detriment of using dihydropyridine CCBs without RAS blockade as an ESRD-prevention strategy in patients with diabetes.

**Ruggenti P, Perna A, Loriga G, et al, for the REIN-2 Study Group.** Blood-pressure control for renoprotection in patients with non-diabetic chronic renal disease (REIN-2): multicentre, randomised controlled trial. *Lancet* 2005;365: 939–46.

Although previous results suggest the benefit of meeting guideline-recommended blood pressure goals to prevent progression of kidney disease, exact blood pressure targets are unclear. The Ramipril Efficacy in Nephropathy (REIN)-2 investigators studied the relative benefit of conservative versus aggressive blood pressure management by adding other antihypertensive agents to ACE inhibitors to prevent adverse renal outcomes. The trial included 338 patients with persistent proteinuria and nondiabetic nephropathy (baseline mean glomerular filtration rate of ~35 ml/min/1.73

m<sup>2</sup>), who were followed for a mean of 19 months. All patients received ramipril up to 5 mg/day and were then randomized to conventional treatment with a target diastolic blood pressure below 90 mm Hg or to intensive treatment with a target systolic blood pressure below 130 mm Hg and a diastolic blood pressure below 80 mm Hg. Patients in the intensive group received felodipine 5–10 mg/day, and all patients could receive any additional antihypertensive agent except a dihydropyridine CCB to achieve their specific blood pressure goal. The study was stopped early because of a clear lack of benefit. Although both groups reached their assigned blood pressure goals and significantly lowered their systolic and diastolic blood pressures from baseline, occurrences of ESRD did not significantly differ. Also, the primary end point of ESRD was not reached when the data were adjusted for prespecified covariates or analyzed by subgroup (e.g., by the degree of proteinuria at baseline). Although aggressive blood pressure goals can be met in patients with nondiabetic renal disease, baseline therapy with dihydropyridine CCBs and ACE inhibitors did not decrease the overall frequency of ESRD.

**Stergiou GS, Makris T, Papavasiliou M, Efstathiou S, Manolis A.** Comparison of antihypertensive effects of an angiotensin-converting enzyme inhibitor, a calcium antagonist and a diuretic in patients with hypertension not controlled by angiotensin receptor blocker monotherapy. *J Hypertens* 2005;23:883–9.

Most patients require more than one antihypertensive drug to control their blood pressure; however, little data are available to determine which combinations are most effective. These investigators examined the relative effects of add-on therapy for hypertension not controlled with full-dose ARB therapy in 64 patients. In a crossover design, therapies were added when patients' blood pressures were not at goal (< 140/80 mm Hg) while they were taking valsartan 160 mg/day. One group received valsartan plus benazepril (ARB–ACE inhibitor) for 5 weeks followed by valsartan plus chlorthalidone (ARBdiuretic) for 5 weeks. The other group received valsartan plus amlodipine (ARB-CCB) followed by valsartan plus benazepril (ARB–ACE inhibitor). Participants underwent 24-hour ambulatory monitoring of blood pressure to assess the effect of each strategy. The ARBdiuretic and ARB-CCB combinations reduced blood pressures more than ARB–ACE inhibitor treatment did. The ARBdiuretic and ARB-CCB combinations yielded similar reductions in blood pressure. Explanations for the finding of a limited benefit from adding an ACE inhibitor to an ARB include an overlapping mechanism of action in blocking angiotensin receptors. However, the addition of an ACE inhibitor to an ARB did reduce blood pressure somewhat; this finding suggests that valsartan 160 mg/day may not achieve 24-hour blockade. Further benefit may be seen if patients are given valsartan 160 mg twice/day or 320 mg/day. Both dosing strategies are used in many countries; however, 160 mg/day is the maximum dose in Greece, where this study was performed.

**Mourad JJ, Waeber B, Zannad F, Laville M, Duru G, Andréjak M, for the Investigators of the STRATHE Trial.** Comparison of different therapeutic strategies in hypertension: a low-dose combination of perindopril/indapamide versus a sequential monotherapy or a stepped-care approach. *J Hypertens* 2004;22:2379–86. (Erratum in *J Hypertens* 2007;25:258.)

The purpose of this study was to determine the best first-line antihypertensive regimen in 533 patients with uncomplicated essential hypertension. Compared were low-dose combination therapy with an ACE inhibitor and a thiazide diuretic, sequential monotherapies from different drug classes



moving from a  $\beta$ -blocker to an ARB to a CCB, and a stepped-care strategy beginning with an ARB followed by an ARB-thiazide combination. Blood pressure was assessed after 6–9 months of therapy. About 62% of patients in the low-dose ACE inhibitor–thiazide combination group reached their goal (blood pressure < 140/90 mm Hg) compared with 49% in the sequential monotherapy group and 47% in the stepped-care group. Rates of adverse events and discontinuation were similar in all three groups. The study was conducted in France, and the dosages for sequential monotherapy and stepped care were lower than what is commonly used in the United States. This variation makes the results difficult to directly apply in countries with other dosing habits.

**Sarnak MJ, Greene T, Wang X, et al.** The effect of a lower target blood pressure on the progression of kidney disease: long-term followup of the modification of diet in renal disease study. *Ann Intern Med* 2005;142:342–51.

The Modification of Diet in Renal Disease (MDRD) study was a large, multicenter trial involving 840 patients with primarily nondiabetic kidney disease and a mean baseline glomerular filtration rate of 24 ml/minute. Patients were randomly assigned to several treatment groups requiring adherence to diets of varying protein content, and hypertension could be treated with any combination of antihypertensive agents. Declines in the glomerular filtration rate were similar between patients with lowered targets for mean arterial pressure (< 92 mm Hg for those  $\leq$  60 yrs and < 98 mm Hg for those  $\geq$  61 yrs) and patients with usual targets (< 107 and < 113 mm Hg, respectively). Because relatively few patients developed kidney failure during the 3-year follow-up in the original trial, the authors published an extended outcome analysis of the study population to specifically look at the longterm effect of lowered blood pressure targets on the occurrence of kidney failure and a composite of kidney failure or death. Outcome data were obtained by using national registry databases, and blood pressure measurements were generally not available for the original participants. Mean follow-up in the extended study was 6.2 years. For the low- versus usual-target group, adjusted HRs were 0.68 ( $p < 0.001$ ) for kidney failure and 0.77 ( $p = 0.0024$ ) for the composite outcome. Original diet allocation, type of kidney disease at baseline, or use of ACE inhibitors did not affect these results. Although this study offered compelling evidence of a long-term benefit from low blood pressure targets for patients with nondiabetic renal disease, notable limitations were its noninterventional nature, its data-collection methods, and the investigators' inability to gather blood pressure readings. All limit any mechanistic understanding of the results obtained.

## Meta-Analyses of Clinical Trials

**Casas JP, Chua W, Loukogeorgakis S, et al.** Effect of inhibitors of the renin-angiotensin system and other antihypertensive drugs on renal outcomes: systematic review and meta-analysis. *Lancet* 2005;366:2026–33.

In many studies, ACE inhibitors and ARBs reduced the progression of both diabetic and nondiabetic nephropathy and reduced the frequency of ESRD. However, the independent effect of the blood pressure–lowering capabilities of ACE inhibitors and ARBs versus other classes of antihypertensives on adverse renal outcomes has not been fully described. This meta-analysis was intended to provide this information from 127 randomized, parallel-design, controlled studies of 73,514 patients with or without diabetes over a mean weighted follow-up of 4.2 years. Comparisons of ACE inhibitors or

ARBs with other classes of antihypertensives on the frequency of ESRD revealed a small but significant benefit in favor of RAS blockers, although this benefit did not extend to results from trials of only patients with diabetes. For urine albumin excretion, ACE inhibitors or ARBs showed a small, significant reduction in risk compared with other blood pressure regimens. However, for changes in glomerular filtration rate and doubling of serum creatinine concentrations, the risk reductions were nonsignificant. All of these results were obtained despite a lack of significant differences in blood pressure changes between groups. Treatment effects for ACE inhibitors or ARBs in preventing nephropathy were larger in placebo-controlled trials than in trials with active-comparator groups. The authors concluded that their results emphasize the relative importance of lowering blood pressure overall for renoprotection versus the specific choice of antihypertensive drug.

**Lindholm LH, Carlberg B, Samuelsson O.** Should  $\beta$  blockers remain first choice in the treatment of primary hypertension? A metaanalysis. *Lancet* 2005;366:1545–53.

$\beta$ -Blockers are widely used in the treatment of primary hypertension. Although they were recommended as first-line treatment in European guidelines at the time of this meta-analysis, they no longer are. A recent analysis of atenolol in patients with hypertension raised the question of relative efficacy of  $\beta$ -blockers compared with other antihypertensives. This analysis included 13 randomized controlled trials of  $\beta$ -blockers versus other agents in 105,951 patients and seven studies of  $\beta$ -blockers versus placebo in 27,433 patients. The relative risk of stroke was 16% (95% CI 4–30%) higher for  $\beta$ -blockers compared with other antihypertensive drugs. Although the relative risk of myocardial infarction was not significantly different between  $\beta$ -blockers and the other drugs, the relative risk of all-cause mortality showed a trend toward favoring the other drugs (relative risk for  $\beta$ -blockers 1.03, 95% CI 0.99–1.08). In the studies where  $\beta$ -blockers were compared with placebo, the relative risk of stroke was reduced by 19%, which was lower than expected, in the patients receiving  $\beta$ -blockers. Conversely, the frequencies of all-cause mortality and myocardial infarction were not significantly different between  $\beta$ -blockers and placebo. Subanalysis of atenolol versus placebo and of other  $\beta$ -blockers versus placebo yielded no significant differences for stroke, myocardial infarction, or all-cause mortality, suggesting that the results were not limited to atenolol. The authors concluded that  $\beta$ -blockers should not be used as first-line treatment for primary hypertension or as reference drugs in future clinical trials.

**Khan N, McAlister FA.** Re-examining the efficacy of  $\beta$ -blockers for the treatment of hypertension: a meta-analysis. *Can Med Assoc J* 2006;174:1737–42. (Erratum in *Can Med Assoc J* 2007;176:976.)

Authors of the previous meta-analysis from 2005 recommended against  $\beta$ -blockade as firstline treatment for primary hypertension. However, three notable design flaws in that meta-analysis warranted its reexamination. First, it excluded large and important clinical trials. Second, survival bias may have affected the use of individual clinical end points (e.g., stroke, myocardial infarction) rather than a composite end point (e.g., major cardiovascular outcomes). Third, the data were statistically ( $p=0.02$ ) and clinically heterogeneous, as hypertension is characterized differently in younger versus older patients. As a result, the present meta-analysis was designed to clarify the effectiveness of  $\beta$ -blockers for the treatment of primary hypertension, with an added emphasis on effects in 50,612 patients younger than 60 years old compared with 95,199 patients aged 60 years or older. The investigators analyzed 21 clinical trials of 145,811 patients and used the composite outcome of death, stroke, or myocardial infarction.  $\beta$ -Blockers reduced the composite outcome in younger

patients (risk ratio 0.86, 95% CI 0.74–0.99) but not in older patients (risk ratio 0.89, 95% CI 0.75–1.05).  $\beta$ -Blockers offered no benefit on any individual end point in younger patients; however, in older patients, they reduced the frequency of stroke (risk ratio 0.78, 95% CI 0.63–0.98) and heart failure (risk ratio 0.54, 95% CI 0.37–0.81) compared with placebo. When  $\beta$ -blockers were compared with an active control, they produced no significant difference in the composite outcome in younger patients, but increased the risk of events in older patients (risk ratio 1.06, 95% CI 1.01–1.10). Individual end points did not significantly differ among younger patients. However, in older patients,  $\beta$ -blockers were associated with a significantly elevated rate of stroke (risk ratio 1.18, 95% CI 1.07–1.30). The authors concluded that the results from the previous meta-analysis were largely driven by the adverse effects in older patients.  $\beta$ -Blockers have been shown to be more effective than placebo and similar to active controls in younger patients. Therefore, they should still be considered an option.

**Bradley HA, Wiysonge CS, Volmink JA, Mayosi BM, Opie LH.** How strong is the evidence for use of beta-blockers as first-line therapy for hypertension? Systematic review and metaanalysis. *J Hypertens* 2006;24:2131–41.

Data from the 2005 meta-analysis also suggested that  $\beta$ -blockers were a poor initial choice for primary hypertension because of their suboptimal effects on stroke outcomes compared with those of other antihypertensives. The aim of this meta-analysis was to compare  $\beta$ -blockers with specific classes of antihypertensives to assess class effects on specific end points, such as stroke and coronary heart disease. The primary outcome was all-cause mortality, and secondary outcomes included fatal and nonfatal coronary heart disease, fatal and nonfatal stroke, cardiovascular mortality, total cardiovascular events, and discontinuation of treatment because of adverse effects. In 13 trials of 91,561 patients,  $\beta$ -blockers were compared with placebo, diuretics, CCBs, and RAS inhibitors. Compared with placebo,  $\beta$ -blockers reduced stroke by 20% (relative risk 0.80, 95% CI 0.66–0.96) and cardiovascular events by 12% (relative risk 0.88, 95% CI 0.79–0.97), with no significant effect on all-cause or cardiovascular mortality. No significant difference was found between  $\beta$ -blockers overall and diuretics in any of the end points; however, propranolol increased the risk of stroke (relative risk 2.28, 95% CI 1.31–3.95), whereas atenolol or metoprolol did not (relative risk 1.00, 95% CI 0.74–1.33).  $\beta$ -Blockers were less effective than CCBs in reducing all-cause mortality (relative risk 1.06, 95% CI 1.00–1.14), stroke (relative risk 1.24, 95% CI 1.11–1.40), and total cardiovascular events (relative risk 1.18, 95% CI 1.08–1.29), but the drugs were similar in their effects on coronary heart disease, cardiovascular mortality, and treatment withdrawal.  $\beta$ -Blockers reduced stroke risk less than RAS inhibitors did (relative risk 1.30, 95% CI 1.11–1.53) and led to more treatment withdrawals (relative risk 1.41, 95% CI 1.29–1.54). The investigators agreed with those from other metaanalyses in that  $\beta$ -blockers should not be used as first-line agents for primary hypertension.

## Clinical Practice Guidelines

**Mancia G, De Backer G, Dominiczak A, et al.** 2007 guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2007;25:1105–87. (Erratum in *J Hypertens* 2007;25:1749.)

The European Society of Hypertension and the European Society of Cardiology have historically

opted not to create guidelines for the diagnosis and treatment of hypertension; instead, they endorsed guidelines from the World Health Organization and the International Society of Hypertension. However, in 2003, the societies decided to create guidelines specifically directed to the European population. These 2007 guidelines update the original publication. In the update, blood pressure goals (< 140/90 mm Hg for most patients) did not change; however, the goal for patients with diabetes, stroke, cardiovascular disease, or renal disease is below 130/80 mm Hg. The guidelines emphasize that any one of five major classes of drugs (thiazide diuretics, calcium antagonists, ACE inhibitors, ARBs, and  $\beta$ -blockers) are suitable for initial therapy alone or in combination, as long as providers consider their patients' comorbid conditions when choosing. Of note,  $\beta$ -blockers are indicated only for the management of clinical events such as a previous myocardial infarction, angina pectoris, heart failure, permanent atrial fibrillation, tachyarrhythmias, or concurrent glaucoma. The report provides a table of other disease states and favored antihypertensive agents, as well as a table for known contraindications to antihypertensives. It also draws attention to antihypertensive treatment in special populations, such as women, the elderly, patients with renal dysfunction, and patients with atrial fibrillation. In addition, they add information regarding home and ambulatory blood pressure monitoring, with advice for patient compliance strategies.

**Rosendorff C, Black HR, Cannon CP, et al.** Treatment of hypertension in the prevention and management of ischemic heart disease: a scientific statement from the American Heart Association council for high blood pressure research and the councils on clinical cardiology and epidemiology and prevention. *Circulation* 2007;115:2761–88. (Erratum in *Circulation* 2007;116:e121.)

The American Heart Association published guidelines in May 2007 as an update to its 2004 recommendations. The blood pressure target remains less than 140/90 mm Hg for most patients. For special populations, such as patients with acute coronary syndromes, CAD or a known CAD equivalent, kidney disease, or diabetes, the target is less than 130/80 mm Hg. Patients with left ventricular dysfunction have a goal blood pressure of less than 120/80 mm Hg. The guidelines provide information about the mechanisms underlying hypertension and CAD, as well as primary prevention strategies. They detail indications for specific drugs in certain populations, and they recommend thiazide-type diuretics, ACE inhibitors, ARBs, and CCBs as first-line therapies.  $\beta$ -Blockers are recommended only for patients who have a history of myocardial infarction or left ventricular dysfunction with or without symptoms of heart failure, unless contraindicated. The guidelines also discuss the management of hypertension in patients with unstable angina, non-STsegment–elevation myocardial infarction, STsegment–elevation myocardial infarction, and heart failure.

**Appel LJ, Brands MW, Daniels SR, Karanja N, Elmer PJ, Sacks FM.** Dietary approaches to prevent and treat hypertension: a scientific statement from the American Heart Association. *Hypertension* 2006;47:296–308.

An update to a 1998 publication, these guidelines were written under the concept that a plethora of dietary factors may affect blood pressure. Detailed within are dietary strategies shown to reduce blood pressure, such as losing weight, decreasing sodium consumption, increasing potassium consumption, moderating alcohol consumption (for individuals who consume alcohol), and consuming the comprehensive Dietary Approaches to Stop Hypertension (DASH) diet. Also

discussed are dietary factors that have limited or uncertain effects on blood pressure, such as fiber, carbohydrates, and various electrolytes.

**Padwal RS, Hemmelgarn BR, McAlister FA, et al, for the Canadian Hypertension Education Program.** The 2007 Canadian hypertension education program recommendations for the management of hypertension: part 1—blood pressure measurement, diagnosis and assessment of risk. *Can J Cardiol* 2007;23:529–38.

**Khan NA, Hemmelgarn B, Padwal R, et al, for the Canadian Hypertension Education Program.** The 2007 Canadian hypertension education program recommendations for the management of hypertension: part 2—therapy. *Can J Cardiol* 2007;23:539–50.

These guidelines were published in 2007, the eighth consecutive year in which the Canadian Hypertension Education Program provided recommendations to health care professionals but the first year in which they made their guidance available to the public. Blood pressure goals remain the same as before, namely, less than 140/90 mm Hg for most patients and less than 130/80 mm Hg for patients with diabetes or renal disease. Emphasis is placed on adherence to drug therapy, dietary salt restriction, the need to assess high normal blood pressure (defined as systolic pressure 130–139 mm Hg and diastolic pressure 85–89 mm Hg) in all adults on a yearly basis, and home monitoring or self-monitoring of blood pressure because of masked hypertension (i.e., blood pressure controlled in the physician's office but not at home). In adults without compelling indications, thiazide diuretics are still recommended as first-line therapy, along with ACE inhibitors (except in African-American patients), long-acting CCBs, ARBs, or  $\beta$ -blockers (in patients aged < 60 yrs). Comorbid conditions with compelling indications for other first-line agents are identified in detailed tables.

## **Nondrug Strategies to Optimize Blood Pressure Control**

### **Pharmacist-Based Strategies**

**Chabot I, Moisan J, Grégoire JP, Milot A.** Pharmacist intervention program for control of hypertension. *Ann Pharmacother* 2003;37: 1186–93.

This article describes a 9-month pilot study to develop a community pharmacist intervention program to improve blood pressure control and to examine factors affecting blood pressure. Four community pharmacies that provided routine pharmaceutical care participated in the intervention group (41 patients), and five in the usual care group (59 patients). The intervention consisted of a computerized decision-aid tool integrated with the pharmacy prescription system that classified patients by their adherence rates and provided written and verbal interventions tailored to individual patients. Patients were classified as adherent if they refilled their antihypertensive prescriptions within 8 days after completing a 30-day supply. Preset questions in the decision-aid tool assisted pharmacists in identifying patient factors that could cause adherence rates to be difficult to ascertain, such as recent hospitalizations and receipt of drug samples. When these factors existed for a patient, adherence was classified as unknown. Patients were stratified by income level. In the high-income group, mean reduction in systolic blood pressure was significantly greater in the intervention versus the usual care

group (7.8 vs 0.5 mm Hg,  $p=0.01$ ), but no significant difference was observed in diastolic blood pressure. Systolic and diastolic blood pressure did not change significantly in the low-income group. The authors did not report overall changes in blood pressure between groups. Although this study was small, it is one of the few published evaluations addressing the involvement of community pharmacists to improve blood pressure control.

**Lee JK, Grace KA, Taylor AJ.** Effect of a pharmacy care program on medication adherence and persistence, blood pressure, and low-density lipoprotein cholesterol: a randomized controlled trial. *JAMA* 2006;296:2563–71.

This single-center study was performed to evaluate the effectiveness of a comprehensive pharmacy care program including patient education and an adherence aid (blister packs) to improve drug adherence in 200 military health care beneficiaries prescribed at least four concomitant drugs on a long-term basis. Phase 1 was a 6-month, prospective study consisting of pharmacist drug counseling, provision of an adherence aid, and regular follow-up visits. In phase 2, patients were randomized to continue the comprehensive pharmacy care program or to receive usual care for an additional 6 months. Changes in blood pressure were evaluated as secondary outcome measures in phase 1 alone. Mean baseline drug adherence was 61.2%. After 6 months, drug adherence increased to 96.9%; this was associated with significant improvements in systolic blood pressure (from 133.2 to 129.0 mm Hg,  $p=0.02$ ) but not in diastolic blood pressure. In phase 2, drug adherence remained at 95.5% in the pharmacist-intervention group and decreased to near baseline (69.1%) in the usual care group. Although the researchers did not evaluate effects of the intervention on clinical events and the study was limited to patients eligible for care at military medical treatment facilities, the findings clearly demonstrated the positive effects of a pharmacy care program on adherence.

**Zillich AJ, Sutherland JM, Kumbera PA, Carter BL.** Hypertension outcomes through blood pressure monitoring and evaluation by pharmacists (HOME study). *J Gen Intern Med* 2005;20:1091–6.

This study was designed to evaluate the effectiveness of a community pharmacist-based program for home blood pressure monitoring. From 12 community pharmacies in eastern Iowa, 64 patients were randomized to receive high-intensity intervention, and 61 to low-intensity intervention. All pharmacists were trained in the proper technique to measure blood pressure. Pharmacists in the high-intensity group received additional education in evidence-based guidelines for managing hypertension. In the high-intensity intervention, patients met with pharmacists face to face for four visits lasting 15–60 minutes each over 3 months. During these visits, patients received specific education about hypertension, including the disease process, drug therapy, lifestyle modification, and technique to measure blood pressure at home. A device to monitor blood pressure was provided after visits 1 and 3, and blood pressure was assessed at home at least once/day for 1 month. The pharmacist calculated mean blood pressures after visits 2 and 4 and used them to develop treatment recommendations that were sent to the patient's provider for implementation. Patients in the low-intensity group were referred to their physicians for evaluation. At 3 months, systolic blood pressure declined by a mean of 13.4 and 9.0 mm Hg from baseline in the high- and low-intensity groups, respectively. Between groups, systolic blood pressure decreased by 4.5 mm Hg, although the difference was not significant, and diastolic blood pressure significantly decreased by 3.2 mm Hg at 3 months. This study showed that intensive education and follow-up by trained community pharmacists

can significantly lower diastolic blood pressure and that this approach may be an option for augmenting hypertension management.

## Nurse-Based Strategies

**Rudd P, Miller NH, Kaufman J, et al.** Nurse management for hypertension. A systems approach. *Am J Hypertens* 2004;17: 921–7.

In this randomized controlled study, researchers evaluated the effect of a nurse-led intervention to control blood pressure compared with usual care in 150 patients with uncontrolled blood pressure or a history of antihypertensive drug treatment. The intervention consisted of baseline counseling in the correct use of home blood pressure cuffs, ways to enhance drug adherence, and recognition of potential drug adverse effects. Nurses obtained approval from physicians to initiate new antihypertensive drugs and could increase dosages of other drugs without prior approval. They also contacted patients by telephone at 1 week and at 1, 2, and 4 months after their enrollment to assess drug adherence and adverse effects. Patients were given home blood pressure cuffs to monitor and record their readings. A member of the research team who was blinded to each patient's group assignment examined the measurements in the clinic at 3 and 6 months after randomization. After 6 months, mean decreases were larger in the nurse-led intervention group than in the usual care group for both systolic (14.2 vs 5.7 mm Hg,  $p < 0.01$ ) and diastolic (6.5 vs 3.4 mm Hg,  $p < 0.05$ ) blood pressure. Drug adherence was greater in the intervention than in the usual care group (80.5% vs 69.2%,  $p = 0.03$ ). Only 10% of the population screened was enrolled; therefore, the generalizability of these results is uncertain. However, this study demonstrated how interventions to augment the delivery of care to patients with hypertension improve not only adherence to antihypertensive therapies but also blood pressure control.

**Schroeder K, Fahey T, Hollinghurst S, Peters TJ.** Nurse-led adherence support in hypertension: a randomized controlled trial. *Fam Pract* 2005;22:144–51.

This study was designed to evaluate the effectiveness of nurse-led adherence support for patients with hypertension compared with usual care. Two hundred forty-five patients with uncontrolled hypertension (blood pressure  $< 150/90$  mm Hg) were randomized to participate in a nurse-led intervention or to continue to receive usual care. Nurses from 21 general practices in England led 20-minute adherence support sessions to discuss patients' problems with their antihypertensive drugs. A 10-minute reinforcement session followed approximately 2 months later. Timing compliance (defined as the number of doses taken divided by the total number of days, multiplied by 100%) at 6 months was the primary outcome measure. No significant differences in timing compliance or in systolic or diastolic blood pressure were observed between the groups. Adherence to antihypertensive drugs in the usual care group was higher than previously reported and may have confounded results. Given these results, the nurse-led adherence support intervention did not seem to add benefits beyond those achieved with usual care.

**Tobe SW, Pylypchuk G, Wentworth J, et al.** Effect of nurse-directed hypertension treatment among First Nations people with existing hypertension and diabetes mellitus: the diabetes risk evaluation and microalbuminuria (DREAM 3) randomized controlled trial. *Can Med Assoc J* 2006;174:1267–71.

This study was designed to assess the effect of a home care nurse following predefined treatment algorithms for patients with hypertension and diabetes compared with usual care from primary care physicians on blood pressure control. Fifty native First Nations patients in Canada were randomly assigned to a home care nurse, and 49 received usual care. The nurse visited with patients at 6 weeks and 3, 6, 9, and 12 months after randomization. The treatment algorithm included the start of irbesartan therapy followed by dosage titration and the addition of hydrochlorothiazide and verapamil as needed to achieve blood pressure goals. At the final visit, systolic blood pressure decreased by a mean of 24 and 17 mm Hg in the nurse and usual care groups, respectively; however, the difference was not significant. Mean diastolic blood pressure reduction was greater in the nurse group compared with the usual care group (11.6 vs 6.8 mm Hg,  $p=0.05$ ). Compared with usual care, intensified management of hypertension by home care nurses significantly improved lowering of diastolic blood pressure but not systolic blood pressure.

**New JP, Mason JM, Freemantle N, et al.** Specialist nurse–led intervention to treat and control hypertension and hyperlipidemia in diabetes (SPLINT): a randomized controlled trial. *Diabetes Care* 2003;26:2250–5.

This randomized controlled study involved 1407 patients with uncontrolled blood pressure or hyperlipidemia who received usual care or usual care plus attendance at respective specialist nurse–led clinics. Nurses conducted clinics every 4–6 weeks and provided lifestyle advice and/or therapeutic intervention according to protocols. The primary outcome was the proportion of patients achieving the specified targets for either intervention. More patients enrolled in the nurse-led clinics than not achieved the primary outcome (odds ratio 1.37, 95% CI 1.11–1.69,  $p=0.003$ ). When the effects on hyperlipidemia and hypertension were evaluated separately, the benefit of the nurse-led clinic remained for hyperlipidemia (odds ratio 1.69, 95% CI 1.25–2.29,  $p=0.0007$ ) but not for hypertension (odds ratio 1.14, 95% CI 0.86–1.51,  $p=0.37$ ). Fewer deaths occurred in the clinic group than in the usual care group (3.2% vs 5.7%, odds ratio 0.55, 95% CI 0.32–0.92,  $p=0.02$ ). This model demonstrated a good method for achieving therapeutic targets relevant to hyperlipidemia and hypertension.

## Patient-Oriented Strategies

**Figar S, Galarza C, Petrlik E, et al.** Effect of education on blood pressure control in elderly persons: a randomized controlled trial. *Am J Hypertens* 2006;19:737–43.

This study was designed to evaluate the effects of two educational models on blood pressure reduction in ambulatory hypertensive patients aged older than 65 years. Sixty patients were randomized to a self-management and patient-empowerment model or to a compliance-based model. Patients in the former group attended workshops to teach self-management and patient empowerment, whereas patients in the latter attended separate workshops that stressed the importance of compliance with medical therapy. The primary outcome measure was the change in systolic blood pressure after 3 months, as measured with 24-hour ambulatory blood pressure monitoring. Systolic blood pressure decreased by a mean of 8 mm Hg in the patient-empowerment group compared with 3 mm Hg in the compliance-based group; blood pressure control was achieved



in 70% and 45% of patients, respectively ( $p=0.045$ ). A self-management education model appears to be superior to compliance-based education with respect to blood pressure control.

**McCraty R, Atkinson M, Tomasino D.** Impact of a workplace stress reduction program on blood pressure and emotional health in hypertensive employees. *J Altern Complement Med* 2003;9: 355–69.

The detrimental effects of elevated blood pressure are well known, and stress is linked to high blood pressure. The purpose of this study was to assess the effect of a workplace-based stress-management program on blood pressure. Thirty-two employees of a technology company who had hypertension were randomly assigned to a stress-reduction intervention or a control group. Participants had to be taking regularly scheduled antihypertensives, or they had to have blood pressures of 140–179 mm Hg systolic or 90–105 mm Hg diastolic. Stress-reduction techniques were taught to the intervention group in one full-day and two half-day sessions over 2 weeks. Participants learned positive refocusing of emotions and emotional restructuring to prevent physiologic and psychological stress responses and to increase mental acuity and emotional stability. Blood pressure, emotional health, and workplace-related measures were evaluated at baseline and after 3 months. At 3 months, systolic blood pressure significantly decreased in the intervention group compared with the control group (by 10.6 vs 3.7 mm Hg). The intervention group also had significant increases in measures of individual well-being and reductions in stress symptoms. The program used multiple techniques; therefore, the results are difficult to attribute to specific methods. In addition, certain techniques applied to particular workplace situations, and no data documented how often the subjects implemented the interventions.

**Schneider RH, Alexander CN, Staggars F, et al.** A randomized controlled trial of stress reduction in African Americans treated for hypertension for over one year. *Am J Hypertens* 2005;18:88–98.

In this randomized trial, investigators studied stress reduction as a method to lower blood pressure in 150 African-American patients with a mean blood pressure above goal at 142/95 mm Hg. Interventions were transcendental meditation for 20 minutes twice/day, progressive muscle relaxation for 20 minutes twice/day, or conventional health education in classes (control). Patients in health education classes were asked to incorporate exercise, restful activities, and healthy cooking into their daily routine. Both transcendental meditation and progressive muscle relaxation involved mental techniques to promote physical relaxation and stress reduction, although their techniques were distinct. After learning the interventions, the patients were asked to practice them at home. After 1 year, transcendental meditation significantly reduced diastolic blood pressures more than progressive muscle relaxation or health education (reductions of 5.67, 2.90, and 2.59 mm Hg, respectively), and it demonstrated a trend toward lowering systolic pressures.

**Tsai JC, Yang HY, Wang WH, et al.** The beneficial effect of regular endurance exercise training on blood pressure and quality of life in patients with hypertension. *Clin Exp Hypertens* 2004;26: 255–65.

The benefit of exercise on blood pressure is well known; however, its effect on quality of life is not well documented. This randomized study included nonobese patients who were not currently exercising, who had a history of hypertension, and who were not receiving any drug therapy to

manage blood pressure. Patients engaged in a moderate-intensity, aerobic exercise program lasting 50 minutes 3 times/week or in no exercise (control). Blood pressure was assessed at baseline and after 10 weeks, as was quality of life (by using the Short Form-36). Perprotocol analysis included 102 patients, whose mean baseline blood pressure was approximately 143/95 mm Hg and mean age was 49 years. Blood pressure decreased by approximately 13/6 mm Hg in the exercise group, compared with a 1-mm Hg decrease in systolic pressure and a 6-mm Hg increase in diastolic pressure in the control group. In addition, quality of life significantly improved in seven of eight domains assessed in the exercise group compared with the control group. The fact that this study was performed in a Taiwanese population may affect our ability to generalize the results to other populations.

## Prescriber-Targeted Strategies

**Roumie CL, Elasy TA, Greevy R, et al.** Improving blood pressure control through provider education, provider alerts, and patient education: a cluster randomized trial. *Ann Intern Med* 2006;145:165–75.

This study was designed to evaluate provider and patient interventions aimed at improving blood pressure control. A total of 182 providers were involved who cared for 1341 patients in Veterans Affairs centers who had at least two uncontrolled blood pressure measurements and who were taking at least one antihypertensive drug. The participants were randomly assigned to one of three groups: provider education consisting of e-mail with a link to the JNC 7 guidelines (group 1); provider education and a one-time, patient-specific electronic hypertension alert (group 2); or provider education, the hypertension alert, and patient education (group 3). In groups 1, 2, and 3, respectively, blood pressure goals were achieved in 42%, 40.9%, and 59.5% of patients ( $p=0.003$  for all comparisons among groups), and blood pressure regimens were intensified in 32.4%, 28.5%, and 29.1%. No significant differences in drug adherence were noted among the groups, as assessed by using drug-refill records. This study confirmed previous results showing inconsistent or minimal changes in blood pressure outcomes with provider education alone. In addition, it highlighted the importance of patient education in improving blood pressure control.

**Murray MD, Harris LE, Overhage JM, et al.** Failure of computerized treatment suggestions to improve health outcomes of outpatients with uncomplicated hypertension: results of a randomized controlled trial. *Pharmacotherapy* 2004;24:324–37.

This 2 x 2 factorial, randomized controlled study of 712 patients with uncontrolled hypertension was designed to assess the effects of evidence-based treatment suggestions made to physicians and/or pharmacists by using a comprehensive electronic medical record system. Patients were randomized to receive physician intervention only, pharmacist intervention only, both, or neither. Physicians and pharmacists received identical suggestions for patient care based on guidelines from the fifth and sixth reports of the Joint National Committee. These suggestions were displayed on the clinician's computer screens used to either write or fill prescriptions. The primary end point was health-related quality of life. Blood pressure measures and drug compliance were secondary end points. There were no significant differences in any of the end points among the four groups. This finding implies that computerized suggestions to support care for patients with hypertension do not improve drug adherence.

**Mitchell E, Sullivan F, Grimshaw JM, Donnan PT, Watt G.** Improving management of hypertension in general practice: a randomized controlled trial of feedback derived from electronic patient data. *Br J Gen Pract* 2005;55:94–101.

The purpose of this study was to evaluate the provision automated feedback derived from computerized patient data to improve the identification, treatment, and control of hypertension. Fifty-two physician groups from Scotland were randomized to receive automated general audits of their patients with hypertension, audit reports plus individualized patient feedback, or no intervention (control). Audit reports were developed by using practice computer systems and consisted of feedback about the number of patients whose blood pressure was recorded and treated, as well as the number of patients who smoked, who had diabetes, or who had a previous stroke. Individualized feedback consisted of each patient's 10-year absolute risk of death from stroke. The primary outcome measure was the percentage of patients with controlled blood pressure (< 160/90 mm Hg). After an adjustment for patient factors, including baseline blood pressure control, this percentage was significantly greater in the audit-plus-feedback group (45.5%; risk ratio 1.72, 95% CI 1.09–2.70) than in the audit-only group (33.5%; risk ratio 0.93, 95% CI 0.55–1.57) or the control group (45.7%; risk ratio 1.0). Despite statistical improvements in blood pressure control in the audit-plus-feedback group, hypertension remained uncontrolled in a considerable number of patients.

**Simon SR, Majumdar SR, Prosser LA, et al.** Group versus individual academic detailing to improve the use of antihypertensive medications in primary care: a cluster-randomized controlled trial. *Am J Med* 2005;118:521–8.

This study was designed to compare group versus individual academic detailing to promote the use of  $\beta$ -blockers or diuretics in managing hypertension. A total of 9820 patients who had newly treated hypertension in the year preceding the intervention were selected from a large health maintenance organization. Patients were allocated to group detailing, individual detailing, or usual care on the basis of the administrative division of the health maintenance organization to which they were assigned. Participating providers received one individual or group academic detailing session at baseline. Patients were assessed for rates of diuretic or  $\beta$ -blocker use at 1 and 2 years after the intervention. In the first year, use increased by 13.2% with group detailing, 12.5% with individual detailing, and 6.25% with usual care. Diuretics and  $\beta$ -blockers were more likely to be used after group and individual detailing than in usual care, although statistical significance was noted only with group detailing. At 2 years, no benefit was observed with individual detailing (odds ratio 1.22, 95% CI 0.92–1.62) or group detailing (odds ratio 1.06, 95% CI 0.80–1.39) compared with usual care. Neither intervention affected blood pressure control. Although the data suggest that both group and individual academic detailing improve the selection of antihypertensive therapy over usual care (nonsignificant trend), the loss of benefit after 1 year may have been due to a lack of reinforcement after detailing.

**Goldstein MK, Lavori P, Coleman R, Advani A, Hoffman BB.** Improving adherence to guidelines for hypertension drug prescribing: cluster-randomized controlled trial of general versus patient-specific recommendations. *Am J Manag Care* 2005;11:677–85.

Investigators compared the use of a general guideline for antihypertensive management with an individualized advisory sent to the physician at each patient clinic visit. This cluster-randomized

controlled trial took place in a university-affiliated Veterans Affairs health care system and included 4500 patients treated by 16 attending physicians or nurse practitioners in the general guideline group and 20 in the individualized advisory group. Individualized intervention improved guideline concordance (percentage change before vs after intervention) to more than twice that observed with general guidelines (10.9% vs 3.8%,  $p=0.008$ ). The individualized advisory regarding antihypertensive drug therapy given at each patient visit was more effective in influencing clinicians' prescribing behaviors than an endorsement of a general practice guideline.

## **$\beta$ -Blocker Controversy**

**Pepine CJ, Handberg EM, Cooper-DeHoff RM, et al, for the INVEST Investigators.** A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The international verapamil-trandolapril study (INVEST): a randomized controlled trial. *JAMA* 2003;290: 2805–16.

The objective of the international verapamil-trandolapril (INVEST) study was to compare the effect of a treatment strategy based on sustained-release verapamil with one based on atenolol on all-cause mortality, nonfatal myocardial infarction, or nonfatal stroke. This was a randomized, open-label trial with blinded end points that included 22,576 patients aged 50 years or older with hypertension and stable CAD. In addition to verapamil and atenolol, trandolapril was recommended for all patients with diabetes, renal impairment, or heart failure. To achieve blood pressure targets from the sixth report of the Joint National Committee, other drugs could be added. Second- and third-line therapies, respectively, were trandolapril and hydrochlorothiazide in the verapamil group or hydrochlorothiazide and trandolapril in the atenolol group. Blood pressure control was similar between the groups during a mean follow-up of 2.7 years, as was the risk of the primary outcome. In the atenolol and verapamil groups, respectively, 82% and 71.6% of patients received an ACE inhibitor (trandolapril or a nonstudy ACE inhibitor) in addition to the primary agent, and 63% and 71% received a diuretic (hydrochlorothiazide or a nonstudy diuretic). These results suggest that a verapamil-based antihypertensive regimen may be as effective as an atenolol-based regimen in patients with stable CAD to reduce major cardiovascular events. The recently recognized inferiority of  $\beta$ -blockers as comparators in hypertension studies complicate application of these results. Moreover, differences between the use of ACE inhibitors and diuretics between the groups make it difficult to draw definite conclusions about any single agent.

**Dahlöf B, Sever PS, Poulter NR, et al, for the ASCOT Investigators.** Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian cardiac outcomes trial-blood pressure lowering arm (ASCOT-BPLA): a multicenter randomised controlled trial. *Lancet* 2005;366:895–906.

Diuretics and  $\beta$ -blockers have typically served as standard treatments for blood pressure in clinical trials, but newer antihypertensives, such as CCBs and ACE inhibitors, may be more effective. Few groups have compared specific combinations of antihypertensives, although the European and American guidelines recommend combination therapy in most patients. In this prospective, controlled study, investigators randomly assigned 19,257 Anglo-Scandinavian patients to receive an atenolol-

based regimen with a thiazide added if needed or an amlodipine-based regimen with perindopril added if needed. The regimens were assessed for their blood pressure–lowering effects in relation to the primary combined end point of nonfatal myocardial infarction and fatal coronary heart disease. After a median follow up of 5.5 years, no significant difference was found between regimens in the primary end point. However, a significant difference was found in favor of the amlodipine-based regimen for several secondary end points, including total cardiovascular events and procedures, all-cause mortality, cardiovascular mortality, and fatal and nonfatal stroke. Of note, one important limitation of this trial was the use of atenolol. Given the results from several recent meta-analyses, use of atenolol as a comparator may have unintentionally influenced the results in favor of the amlodipine-based regimen.

**Carlberg B, Sameulsson O, Lindholm LH.** Atenolol in hypertension: is it a wise choice? *Lancet* 2004;364:1684–9. (Erratum in *Lancet* 2005;365:656.)

This systematic review was conducted to evaluate the effectiveness of atenolol as an antihypertensive agent. Four trials were identified that compared atenolol with placebo (6825 patients followed for a mean of 4.6 yrs) and five trials compared atenolol with other antihypertensive drugs (17,671 patients). No significant differences in cardiovascular outcomes were discovered between atenolol and placebo, although rates of stroke tended to be lowest in the atenolol group (relative risk 0.85, 95% CI 0.89–1.01). Compared with other antihypertensive treatments, atenolol provided no significant difference in blood pressure control but increased the risk of total mortality (relative risk 1.13, 95% CI 1.02–1.25). The risk of stroke and cardiovascular mortality also tended to rise with atenolol therapy. These results cast doubt on the use of atenolol as an antihypertensive and on its use as a reference drug in antihypertensive trials.

**Messerli FH, Mancia G, Conti CR, et al.** Dogma disputed: can aggressively lowering blood pressure in hypertensive patients with coronary artery disease be dangerous? *Ann Intern Med* 2006;144:884–93.

This post hoc analysis of the INVEST study was performed to evaluate the effects of aggressively lowering blood pressure on adverse outcomes in patients with CAD. A total of 22,576 patients with hypertension and CAD were randomly assigned to receive treatment based on sustained-release verapamil or atenolol. An unadjusted, quadratic proportional-hazards model was used to evaluate the relationship between blood pressure during treatment and adverse outcomes (death, myocardial infarction, or stroke). The relationship between blood pressure and the primary outcome of all-cause death and total myocardial infarction was J shaped, particularly that for diastolic blood pressure, which persisted after an adjustment for baseline covariates (age, sex, race, ethnicity, and certain preexisting medical conditions). In contrast, the risk for stroke was not correlated with a low diastolic blood pressure. Excessive reduction in diastolic blood pressure (nadir < 74 mm Hg) should be avoided in patients with CAD who are treated for hypertension.

## Miscellaneous Topics of Interest

**Gradman AH, Alfayoumi F.** From left ventricular hypertrophy to congestive heart failure: management of hypertensive heart disease. *Prog Cardiovasc Dis* 2006;48:326–41.

This comprehensive review article describes what is known about the prevalence, risk factors, pathology, and therapeutic options for hypertensive heart disease defined as left ventricular hypertrophy. Of most importance, it elucidates unknown aspects about the identification and management of this common complication. Depending on the severity of hypertension, left ventricular hypertrophy is present in 20–60% of patients with untreated blood pressure. Other than age, left ventricular hypertrophy is the most potent predictor of negative cardiovascular outcomes. It is an adaptive response to chronically increased cardiac workload and results in not only myocyte hypertrophy but also myocardial fibrosis and thickening of the intramyocardial coronary arteries. In addition to increased pressure, neurohormones and genetic factors play a role in the development of these structural changes. Drugs that affect the RAS appear to be most effective for inducing regression of left ventricular hypertrophy, and observational data suggest that pharmacologically treated hypertension decreases the frequency of this complication by one third. As left ventricular hypertrophy progresses, it continues to adversely affect diastolic function, decreasing left ventricular distension, filling, and relaxation. The resultant increase in end diastolic pressure raises left atrial pressure and causes symptoms of diastolic heart failure: pulmonary edema, dyspnea, and exercise intolerance. Observational data indicate that pharmacologically treated hypertension decreases the development of diastolic heart failure by 50%. Although results are inconclusive at this time, diuretics, ACE inhibitors and ARBs are the preferred antihypertensive agents after diastolic heart failure develops. Of all hospitalizations for heart failure, half are due to diastolic dysfunction. The 1-year readmission rate for diastolic heart failure is equal to that for systolic heart failure (~50%), and the 1-year mortality rate is approximately 6% (compared with 12% with systolic dysfunction).

**Hermida RC, Smolensky MH.** Chronotherapy of hypertension. *Curr Opin Nephrol Hypertens* 2004;13:501–5.

The article succinctly reviews the principles of chronotherapy and summarizes the available data regarding chronotherapeutic effects of individual pharmacologic agents. An excessively accelerated morning rise in blood pressure is known to be associated with stroke. In addition, absence of the normal 10–20% decline in nocturnal blood pressure is associated with left ventricular hypertrophy, myocardial infarction, stroke, and albuminuria. Conversely, an excessive (> 20%) decline in nocturnal blood pressure, sometimes pharmacologically induced, is associated with stroke and fractures due to syncopal episodes. With chronotherapy, clinicians strive to time the administration of antihypertensive drugs to attenuate a rapid rise in morning blood pressure, to normalize the daytime and nighttime blood pressures to their normal circadian pattern, and to avoid excessive lowering of blood pressure at night. As a therapeutic goal, normalization of circadian blood pressure is certainly in its infancy; however, data support its benefit in patients with clinically significant renal disease. Activity levels of many processes that affect drug absorption, distribution, and metabolism vary throughout the day. For instance, gastric pH, gastrointestinal motility and blood flow, and liver enzyme activity fluctuate over 24 hours and affect the pharmacokinetic characteristics of many drugs. Despite fairly detailed knowledge about these processes and their effects on pharmacokinetics, rarely has the timing of drug administration been the focus of an investigation with clinical outcomes. The authors review the sparse chronotherapeutic data available according to drug classes, including ACE inhibitors, ARBs,  $\alpha$ -adrenergic antagonists, and CCBs. They also provide dosing strategies for each class to maximize chronotherapeutic principles. Evidence suggests that low-dose aspirin reduces blood pressure when it is administered at bedtime instead of in the morning.

**Van Tassel BW, Munger MA.** Aliskiren for renin inhibition: a new class of anti-hypertensives. *Ann Pharmacother* 2007;41:456–64.

Aliskiren is the first of a new class of antihypertensives called renin inhibitors. To date, investigators have reported results from three trials (each < 8 wks in duration) in 867 patients to evaluate the effect of this drug on blood pressure. In these trials, aliskiren 150–300 mg/day reduced systolic blood pressure by 8–16 mm Hg and diastolic blood pressure by 11–12 mm Hg compared with placebo. Reductions in systolic blood pressure were similar for aliskiren 150 and 300 mg/day and losartan 100 mg/day. Another comparison of aliskiren 150, 300, and 600 mg/day with irbesartan 150 mg/day showed similar decreases in systolic blood pressure between the drugs; however, aliskiren 300 and 600 mg/day reduced diastolic blood pressure more than irbesartan ( $p < 0.01$ ). The adverse effect profile of aliskiren was similar to that of placebo, and the drug has shown no proclivity to clinically significant drug interactions. Longterm data are needed, as only one published abstract provides evidence of the effects of aliskiren after 8 weeks.

**Krousel-Wood M, Muntner P, Jannu A, Desalvo K, Re RN.** Reliability of a medication adherence measure in an outpatient setting. *Am J Med Sci* 2005;330:128–33.

This study was designed to assess the reliability of the Hill-Bone Compliance scale in 239 community-dwelling patients with hypertension. The scale was developed as a self-administered tool for health care providers to quickly assess compliance with antihypertensive therapy. It consists of 14 items in the behavioral domains of taking drug therapy, appointment keeping, and reduced sodium intake. Scores range from 14–56, with high scores indicating poor compliance. Reliability was validated by using a measure to determine internal consistency. Although the Hill-Bone Compliance scale had good internal consistency (Cronbach  $\alpha$  of 0.68), its results were not correlated with pharmacy refill records or other measures of compliance to assess validity. However, this survey may be a useful tool for health care providers to use in practice, in addition to other traditional measures of compliance, to assess patient compliance with antihypertensive therapy.

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