Analysis of Recent Papers in Hypertension

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EFFECTS OF A CALCIUM CHANNEL BLOCKER AND A STATIN-BASED TREATMENT REGIMEN IN THE ANGLO-SCANDINAVIAN CARDIAC OUTCOMES TRIAL

Coronary heart disease (CHD) remains the leading cause of morbidity and mortality in the United States. Almost all individuals with CHD have 1 or more risk factors, including hypertension, dyslipidemia, glucose intolerance, and smoking. The number of cardiovascular (CV) risk factors present in each patient's risk profile significantly influences age-adjusted rates for CV death in a synergistic fashion. To favorably address global CV risk, strategies that incorporate multiple risk factor improvement rather than a silo approach to risk factor reduction should be utilized for optimal results. In the present prespecified analysis, investigators sought to demonstrate the possible synergistic effects of a statin, atorvastatin, and specific blood pressure (BP)–lowering treatments in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT).

The lipid-lowering arm of ASCOT (ASCOT-LLA) was part of a larger study, the ASCOT-BP-Lowering Arm (ASCOT-BPLA), which enrolled 19,257 patients with hypertension from the United Kingdom, Ireland, and several Northern European countries. Patients were eligible for this industry-sponsored, investigator-initiated and -led, prospective, randomized, controlled trial if they were 40 to 79 years of age with hypertension and several additional CV risk factors, but were free of CHD on entry. Eligible patients had to be untreated for hypertension with a systolic BP of at least 160 mm Hg or diastolic BP of at least 100 mm Hg on treatment, with a systolic BP of at least 140 mm Hg or diastolic BP of at least 90 mm Hg (80% were on previous antihypertensive treatment). In addition, they had to have at least 3 of the following risk factors: history of smoking, left ventricular hypertrophy or other prespecified abnormalities on electrocardiography, a first-degree relative with premature CHD, age older than 55 years, microalbuminuria or proteinuria, non–insulin-dependent diabetes, peripheral vascular disease, previous stroke or transient ischemic attack, male sex, or ratio of plasma total cholesterol to high-density lipoprotein (HDL) cholesterol of 6 or higher. Exclusion criteria included previous myocardial infarction (MI), currently treated angina, cerebrovascular event within the past 3 months, fasting serum triglycerides exceeding 4.5 mmol/L, heart failure, uncontrolled arrhythmias, or any clinically important hematologic or biochemical abnormalities.

Following a 4-week run-in period, subjects were randomized to either a calcium channel blocker (CCB)-based regimen with amlodipine as the initial antihypertensive therapy or a β-blocker–based regimen with atenolol as initial antihypertensive therapy. If the BP was not controlled on amlodipine, 10 mg once daily, the angiotensin-converting enzyme inhibitor perindopril, titrated up to a maximum of 8 mg daily, was added to the CCB-based regimen (n=9639). If the patient's BP was not controlled on atenolol, 100 mg once daily (n=9618), a thiazide diuretic, bendroflumethiazide + potassium, titrated up to 2.5 mg, was added. If needed, the α_1-antagonist doxazosin, up to 8 mg, was added as a third agent to each arm of the trial to reach the target BP of less than 140/90 mm Hg (less than 130/80 mm Hg if diabetic). Those individuals with a fasting cholesterol of up to 6.5 mmol (250 mg/dL) who were currently untreated with a statin or fibrate

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were further randomized, using a 2 × 2 factorial design, to either 10 mg atorvastatin daily or matching placebo (n=10,305) (ASCOT-LLA).

The primary end point of both ASCOT-LLA and ASCOT-BPLA was the composite of nonfatal MI (including silent MI) and fatal CHD. Secondary end points included nonfatal or fatal stroke and a number of additional composite CV end points. Prespecified tertiary objectives included an evaluation of any synergy between the BP-lowering and lipid-lowering regimens, the subject of the present publication.

Time to first events in the atorvastatin and placebo groups were compared on an intention-to-treat basis until the closeout of ASCOT-LLA (median follow-up, 3.3 years) using the log-rank and Cox proportional hazard models. Complete information was available for 98.8% of persons who were randomized. Baseline characteristics were similar among the 4 groups: amlodipine-based + atorvastatin; amlodipine-based + placebo; atenolol-based + atorvastatin; and atenolol-based + placebo. The mean age of patients was 63 years, with 95% white, 82% men, and an average body mass index (BMI) of 29 kg/m^2. Baseline risk factors were equally distributed in all 4 groups.

Calculated low-density lipoprotein (LDL) cholesterol was reduced 45.6 mg/dL after 1 year and 38 mg/dL at the end of the study in patients receiving the statin. There were no differences between the amlodipine-based and atenolol-based regimens in the extent to which total and LDL cholesterol were lowered by atorvastatin. Among patients randomized to the amlodipine-based regimen, HDL cholesterol increased slightly both on atorvastatiin and on placebo, whereas in the atenolol-based group, there was a small reduction in HDL cholesterol both with atorvastatin and with placebo. Compared with placebo, atorvastatin produced a small but similar increase in HDL cholesterol in both the amlodipine- and the atenolol-based regimens. Atorvastatin produced similar reductions in serum triglycerides among patients allocated to either amlodipine- or atenolol-based therapy.

Mean BP levels were similar with atorvastatin and placebo (138.3/80.4 mm Hg and 138.4/80.4 mm Hg, respectively). BP was controlled to target levels below 140/90 mm Hg in 58% of nondiabetic patients and below 130/80 mm Hg in 31% of diabetic patients. On average, BP fell 2.9/2.0 mm Hg more on amlodipine-based then atenolol-based treatment; these differences were similar among those allocated to either atorvastatin or placebo.

Atorvastatin significantly reduced the incidence of CHD events and strokes in subjects with well-controlled hypertension and no underlying CHD. Compared with placebo, the use of atorvastatin, 10 mg, produced a 36% reduction in the primary end point of nonfatal MI and fatal CHD (hazard ratio, 0.64; 95% confidence interval [CI], 0.50–0.83; *P*=.0005), and the primary end point was reduced by 53% among those randomized to the amlodipine-based regimen (HR, 0.47; CI, 0.32–0.69; *P*<.0001) and 16% with the atenolol-based regimen (HR, 0.84; CI, 0.60–1.17; *P*=.30). The difference between these risk reductions with atorvastatin were not significant. Compared with placebo, atorvastatin reduced the relative risk of total CV events and procedures among individuals allocated to the amlodipine-based treatment by 27% (HR, 0.73; CI, 0.60–0.88; *P*=.001) and 15% (HR, 0.85; CI, 0.71–1.02; *P*=.079) among those allocated to atenolol-based treatment. Again, the difference between these effects was not significant (heterogeneity *P*=.25) and is due entirely to the observed difference in the primary end point. The effects of atorvastatin in subjects randomized to amlodipine-based treatment on nonfatal or fatal strokes (HR, 0.69; CI, 0.45–1.06; *P*=.09) compared with those randomized to atenolol-based treatment (HR, 0.76; CI, 0.53–1.08; *P*=.13) were also not significantly different from each other (heterogeneity *P*=.73).

The findings of an apparent interaction between atorvastatin and an amlodipine-based regimen in the prevention of CHD events are of borderline significance. As the authors state, this may be due at least in part to chance. Future studies must be performed to better understand why the apparent interaction between the specific antihypertensive agents used and statin-based therapy with atorvastatin appears to benefit CHD events but not other CV end points. The authors suggest that this may be due to atorvastatin's effects on plaque stability rather than its effects on other CV end points where the underlying pathophysiologic processes are more diverse.—*Sever P, Dahlof B, Poulter N, et al, on behalf of the ASCOT Steering Committee Members. Potential synergy between lipid-lowering and blood-pressure-lowering in the Anglo-Scandinavian Cardiac Outcomes Trial.* Eur Heart J. *2006;27:2982–2988.*

COMMENT

The ASCOT study was conducted using a 2 × 2 factorial design, which included a BP-lowering arm (ASCOT-BPLA) and a lipid-lowering arm (ASCOT-LLA). The ASCOT-BPLA trial was stopped early by its data monitoring safety board because of an increase in total mortality seen in the

atenolol-based regimen compared with the amlodipine-based regimen. As in previous studies, atenolol, when given once a day, was not an acceptable comparator for the initial treatment of hypertension. When the trial was stopped after a mean of 3.3 years' follow-up, there was a nonsignificant 10% reduction in the primary outcome of nonfatal MI (including silent MI) and fatal CHD in favor of the amlodipine-based therapy. Amlodipine-based therapy was also associated with favorable reductions in several secondary end points, including nonfatal MI (excluding silent MI) and fatal CHD, CV death, and all-cause death.

In addition to assessing the benefits of the 2 antihypertensive treatment strategies, ASCOT-LLA was designed to evaluate atorvastatin, 10 mg daily, or placebo among the 10,305 subjects of the ASCOT-BPLA subset with total cholesterol up to 250 mg/dL. As with the BP study, ASCOT-LLA was terminated early by the safety board, at which time patients on atorvastatin showed a 36% reduction in the incidence of nonfatal MI and fatal CHD compared with placebo.

In this latest analysis of ASCOT-LLA, the effects of atorvastatin compared with placebo among patients in each of the 2 BP-lowering groups were compared in a prespecified analysis to evaluate whether any potential interaction between the antihypertensive and lipid-lowering regimens could have contributed to the differences seen in ASCOT-BPLA. Of the patients randomized to atorvastatin on amlodipine-based therapy, the primary outcome of nonfatal MI and fatal CHD was reduced by 53% compared with a reduction of only 16% in those randomized to atorvastatin and atenolol-based therapy; this difference, however, was of only borderline significance in favor of amlodipine. There were no significant differences between the effects of atorvastatin on total CV events or strokes between those assigned amlodipine-based or atenolol-based BP-lowering therapy.

Amlodipine, a dihydropyridine CCB, may have unique antiatherosclerotic effects. Amlodipine, as well as other antihypertensive agents, has been shown to favorably affect endothelial function, increasing the production of nitric oxide and reducing the local production of free oxygen radicals, including superoxide anion. While all CCBs may reduce the oxidation of LDL cholesterol and inhibit the entry of LDL into the vessel wall, amlodipine may have specific effects on monocyte migration and adhesion to the endothelium that allows it to be antiatherosclerotic; amlodipine has been shown to reduce progression of carotid intimal-medial thickness. The authors of the present analysis believe that specific effects of amlodipine and the interaction reported between this agent and a statin accounts for their ability to stabilize atherosclerotic plaque (reduction in nonfatal MI and fatal CHD events) when used together. The fact that there was no difference in stroke or other vascular end points was felt to occur because the atherosclerotic process in those vascular beds is more diverse and more dependent on differences in BP than events that occur in the coronary vasculature. In addition, because the benefit of atorvastatin was seen in the amlodipine-based regimen beginning at 1 month and became significant within 3 months before other antihypertensive agents were added, it is possible that there may be specific synergistic effects between atorvastatin and amlodipine. Clearly, further studies are required before evidence of this interaction can be accepted.

Other statin-based trials including the Heart Protection Study, the Prospective Pravastatin Pooling Project, and the Cholesterol Treatment Trialists meta-analysis failed to show any favorable interaction between the various statin and antihypertensive agents used. Since on-treatment triglyceride levels were higher and HDL cholesterol levels were lower in the atorvastatin/atenolol-treated patients, and because the central BP-lowering effects of atenolol may be different than those with amlodipine, future studies must confirm the hypothesis-generating questions about synergy with these agents. As the authors rightly point out, they might just represent the play of chance.

HYPERTENSION PREVALENCE INCREASES AND HYPERTENSION CONTROL RATES IMPROVE IN THE UNITED STATES: 2003–2004

The National Health and Nutrition Examination Survey (NHANES) has long been used as the standard for tracking rates of BP awareness, treatment, and control in the United States. According to data from NHANES 1999–2000, approximately 58 million US adults, or 28.7% of the population, had hypertension, with 69% of patients with hypertension aware of their condition, 58% receiving treatment, and 31% having their BP controlled to below 140/90 mm Hg. During the same time period, if a more liberal definition of hypertension was used, defining it as having been told at least twice by a health care professional that you have hypertension (regardless of actually being on antihypertensive medication or having a BP at least 140/90 mm Hg), approximately 65 million

US adults would be considered hypertensive. Data from NHANES 2003–2004 recently became available. In the present report, this information was compared with the NHANES 1999–2000 data to analyze trends in the prevalence, awareness, treatment, and control of hypertension according to current treatment goals.

NHANES has been administered as a continuous survey program since 1999. In the most recent NHANES program, each participant (N=17,061) who was at least 18 years of age had BP measured 3 or 4 times manually by a trained operator using a mercury sphygmomanometer according to a standard protocol. The BP for each participant was determined as the average of all readings except the initial reading, which was discarded. Hypertension was defined as an average BP at least 140/90 mm Hg or current use of antihypertensive medications (regardless of the presence or absence of diabetes mellitus, chronic kidney disease, or other comorbid conditions). BP was considered treated if the participant reported taking antihypertensive medication(s) at the time of the survey and was considered controlled if the average BP was below 140/90 mm Hg in nondiabetics and below 130/80 mm Hg in patients with diabetes. The prevalence, awareness, treatment, and control rates were age-adjusted by direct standardization to the US 2000 population based on census data. BMI was calculated as weight in kilograms divided by the square of height in meters. Sampling weights were used to adjust for nonresponse bias and oversampling of blacks, Hispanics, and the elderly. The 2003 to 2004 NHANES data were compared with the 1999 to 2000 data, both of which were collected using the same methodology.

After excluding 2408 participants who were either interviewed but not examined or had missing BP or weight information, data on 14,653 individuals were analyzed (4749 in 1999–2000, 5032 in 2001–2002, and 4872 in 2003–2004). There were fewer people in the 18 to 39 age group and more people in the 40 to 59 age group in 2003 to 2004. Among the 2003 to 2004 participants, the prevalence of hypertension was 29.6% (age-adjusted), which represented a nonsignificant increase since 1999 to 2000 (28.6% age-adjusted). In 2003 to 2004, 75.7% (66.5% age-adjusted) of people with hypertension were aware of their diagnosis, 65.1% (53.7% age-adjusted) were treated, and 36.8% (33.1% age-adjusted) were controlled. Among patients being treated for hypertension, 56.6% (63.9% age-adjusted) were controlled. These awareness and treatment rates represent a nonsignificant increase from 1999 to 2000 (68.7%, 63.0% age-adjusted and 58.2%, 47.3% age-adjusted, respectively). Importantly, the overall BP control rate increased significantly from 29.2/2.3% in 1999 to 2000 to 36.8/2.3% in 2003 to 2004 (P=.02; P=.006 after age-adjustment). The age-adjusted increase in BP control rate was 8.1% (95% CI, 2.4%–13.8%).

As in 1999 to 2000, the prevalence of hypertension in 2003 to 2004 increased with increasing age and BMI, but was not associated with gender differences. Non-hispanic blacks once again had the highest prevalence of hypertension. Control rates were lowest in middle-aged Mexican American women (27.8%). Among those actually receiving antihypertensive treatment, control rates were lowest in older black women (39.8%). Between 1999 to 2000 and 2003 to 2004, there were no significant changes in the awareness and treatment rates by sex or race/ethnicity. Control rates increased significantly in both men (from 25.5%/2.3% to 33.3% /2.8%, P=.03) and women (from 24.9%/2.9% to 35.2%/4.4%, P=.05) and in non-Hispanic black men (from 18.8%/2.6% to 29.9%/3.5%, P<.05) and Mexican Americans (from 13.6%/2.7% to 26.5%/5.1%, P<.05). The increase in control rates was especially striking among Mexican American men (from 8.7%/2.2% to 31.1%/7.0%, P=.002). Awareness, treatment, and control rates all increased in patients who were at least 60 years of age (P<.01). There was also a significant increase in BP control among people who were obese (BMI at least 30 kg/m^2).

No change in the prevalence of hypertension was noted between the 1999 to 2000 and 2003 to 2004 samples, but there were significant improvements in BP control rates, especially among black men, Mexican American men, and the elderly. The authors suggest that public health measures or changes in clinical practice are headed in the right direction.—*Ong KL, Cheung BMY, Man YB, et al. Prevalence, awareness, treatment, and control of hypertension among United States adults, 1999–2004*. Hypertension. 2007;*49:69–75*.

COMMENT

NHANES is a large health and nutritional survey of the US civilian noninstitutionalized population. It is useful for monitoring trends in the health status that come about as a result of public health measures or changes in clinical practice. Data from NHANES been invaluable specifically in examining trends in the awareness, treatment, and control of hypertension for nearly 5 decades. Strengths

of NHANES include its statistical power, quality control, and most importantly the consistency of design over time. Using advanced statistical techniques, NHANES provides us with snapshots of the overall health and nutritional status of the US population over time. According to information available on the NHANES Web site (www.cdc/gov/nhanes.org) each participant represents approximately 50,000 US residents. Participants are selected through a complex statistical process using US census information. NHANES breaks down the US population into communities, with each community further divided into neighborhoods. Representative neighborhoods are subsequently selected based on census information of households within these neighborhoods selected at random to participate. About 15 counties are selected each year and, since 1999, NHANES has conducted surveys continuously. After obtaining informed consent, each selected individual (about 5000 each year) undergoes a detailed interview at home that includes demographic, socioeconomic, dietary, and health-related questions. Participants are also invited to a mobile examination center, consisting of 4 interconnected vans, where trained administrative personnel conduct medical and dental examinations, physiologic measurements (including BP), and laboratory tests. While information on BP may be the most widely disseminated information collected by NHANES, important information is also ascertained about many other disease states. As such, NHANES is designed to obtain a representative sample of the health and nutrition status of the US population.

After decades of slow but steady improvement in the awareness, treatment, and control of hypertension, NHANES 1999–2000 suggested a relative plateau had been reached in many important BP variables. The most recent NHANES BP data reported from 2003 to 2004, however, confirm important advances in awareness, treatment, and control of hypertension. While the prevalence of hypertension has not increased since 1999, improvements in BP control rates for populations that have traditionally been difficult to treat, such as the elderly, non-Hispanic blacks, and Mexican Americans are especially encouraging and suggest that public health efforts have been effective. While the overall control rate of 36.8% cited in this report is the most relevant for comparing rates over time and will likely be the most widely disseminated number from this report, the age-adjusted rate of 33.1% is more representative of the overall US population. Increasing rates of control among patients receiving antihypertensive therapy also suggest that practitioners involved in treating hypertension are becoming more effective in getting their patients to goal. Among treated hypertensives, control rates have risen around 3%, with a control rate of 56.6% among those on antihypertensive medication; these rates approach control rates seen in major clinical trials. While the authors of this report suggest a number of potential explanations for the improvements observed, any purported explanations should be treated as hypothesis-generating only.

These data are cause for some celebration, but we must recognize that there is still considerable room for improvement. Two thirds of persons with hypertension in the United States still do not have adequate BP control. If we are going to reach the Healthy People 2010 BP control goal of 50%, we need to accelerate the rate of improvement. While it is tempting to focus the majority of our attention on intensifying therapy among hypertensives already on treatment, we must continue to emphasize awareness of hypertension through public health, community-based screenings, and effective educational campaigns. Decreasing the prevalence of hypertension through greater attention to lifestyle modification has potential benefit if we are to improve the overall health of the US population. High-risk populations should be targeted, for evidence of improved BP control exists in the current report. If we are to make a significant dent in the prevalence of hypertension, we must continue to emphasize weight control and waist circumference reduction. The hypertension community anxiously awaits future reports from NHANES that will serve as important report cards on how well we are identifying, treating, and controlling hypertension in the United States. As stated in the editorial by Dr Ted Kotchen, "we have miles to go before we sleep."[1]

REFERENCE

1 Kotchen TA. Hypertension control: trends, approaches, and goals. *Hypertension*. 2007;49:19–20.