Hypertension Highlights

New Definitions and New Classes of Antihypertensive Drugs Show Promise

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Introduction

Heart rate variability has long been known to be more of a risk predictor than heart rate, per se, but this month a study evaluates blood pressure variability -- and finds that it is and it isn't significant. Plus, inhibition of the renin-angiotensin system with angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) has proven efficacy - and now, this month, we have the phase 3 clinical results for a new class of antihypertensive agent (aliskiren) that inhibits renin directly. Plus, what about phosphodiesterase type 5 inhibitors (eg, sildenafil) as antihypertensive agents?  Moreover, this month there were reports of a "signal" that diuretics appear to cause breast cancer, at least in some women. Finally, a device to treat hypertension -- and the Chinese begin to deal with their hypertensive population.

Blood Pressure Variability Not an Independent Predictor of Outcome in Treated Hypertensive Patients

It has long been noted that it is not heart rate, per se, that correlates with cardiovascular pathology, but rather the ability of the heart rate to vary appropriately and return to basal values quickly that is the sign of a healthy heart. However, few studies have examined the relationship between blood pressure variability and prognosis in people with treated or untreated hypertension, and only one has investigated this relationship in patients with treated hypertension alone. Now Italian investigators have shown that although treated hypertensive patients with high blood pressure variability have a higher rate of cardiovascular events than those with low blood pressure variability, when other relevant prognostic factors such age, smoking habit, diabetes, low-density lipoprotein (LDL) cholesterol, previous events, etc, are taken into account, blood pressure variability is not an independent predictor of outcome. These findings are published in the October issue of the American Journal of Hypertension.[1]

Sante D. Pierdomenico, MD, and colleagues at the Università "Santissima Annunziata," Chieti, studied a total of 1472 treated hypertensive patients from the local region who were participating in a larger study of ambulatory blood pressure monitoring (ABPM). Patients with uncontrolled hypertension on single therapy or with secondary hypertension were excluded from the study. ABPM was performed over 1 day of typical activity. Readings were obtained at 15-
minute intervals from 6 AM to midnight and at 30-minute intervals from midnight to 6 AM.

Average values (± standard deviation) were calculated for daytime (awake period), nighttime (sleep period), and 24-hour systolic and diastolic blood pressures (SBP and DBP) for each patient. Subjects with a standard deviation for daytime and nighttime SBP above or below the median of the population were classified as having high or low blood pressure variability, respectively. Because these values were above and below the median, this effectively divided the study population into 2 halves, and when this was calculated, this revealed that 738 and 734 patients had low and high daytime blood pressure variability, respectively, and 739 and 733 had low and high nighttime blood pressure variability, respectively.

Compared with patients with low variability for both daytime and nighttime blood pressures, the patients with high blood pressure variability were significantly older, had higher clinic, daytime, nighttime, and 24-hour SBP values, and included fewer patients with a family history of premature cardiovascular disease \((P < .05\) for all values). On the other hand, the patients with higher daytime blood pressure variability also had higher LDL-cholesterol, included fewer men and patients on single-drug therapy, and a higher prevalence of left ventricular (LV) hypertrophy \((P < .05\) for all values). It was also noted that more patients with high day- and nighttime blood pressure variability were taking ACE inhibitors.

Follow-up was carried out in these patients at the hospital outpatient clinic or by the patients' family physicians over a mean duration of 4.88 ± 2.9 years. During this time, 119 fatal or nonfatal cardiovascular events occurred (108 first and 11 second events), including 31 myocardial infarctions (MIs), 19 coronary revascularizations, 9 cases of heart failure requiring hospitalization, 49 strokes, 8 peripheral revascularizations, and 3 cases of renal failure requiring analysis. Event rates, calculated per 100 patient-years, were higher in patients with high blood pressure variability.

When looking only at daytime blood pressure variability, event rates per 100 patient-years were approximately double for subjects with high vs low variability \((2.01 \text{ vs } 1.19, \text{ respectively})\), and for nighttime blood pressure variability the corresponding values were 2.05 and 1.2, respectively. Event-free survival was significantly higher in the low blood pressure variability groups \((P = .006\) for both daytime and nighttime blood pressures). However, after adjusting for age, gender, family of history of premature cardiovascular disease, smoking habit, previous cardiovascular events, body mass index (BMI), clinic blood pressure, LDL cholesterol, creatinine, diabetes, LV hypertrophy, day or nighttime blood pressure, blood pressure variability group, and antihypertensive drug class, blood pressure did not emerge as an independent predictor of cardiovascular events. By contrast, even after adjustment, smoking habit, LDL-cholesterol level, diabetes, previous events, LV hypertrophy, and day/nighttime SBP all remained as predictors of events. Separate analysis of cardiac and cerebrovascular events showed the same trend.

Dr. Pierdomenico and his colleagues point out that their results cannot be applied to non-Caucasian ethnic groups, which were not included in their study. They also suggest that different results might be obtained if blood pressure variability values were evaluated by invasive and beat-to-beat blood pressure monitoring, or if another, more complex index of variability was used. An index called “average real variability,” based on the total variability by real analysis in mathematics, was recently proposed as being more reliable than using standard deviation in evaluating the prognostic significance of blood pressure variability.\(^2\)

**New Data on the Oral Renin Inhibitor Aliskiren in Patients With Hypertension**

At the recent World Congress of Cardiology (WCC) in Barcelona, Spain, new data were presented on aliskiren, the oral renin inhibitor that is pending approval for the treatment of hypertension in the United States and Europe.\(^3\) (See Medscape's Conference Coverage of WCC.) The data, from phase 3 clinical trials with aliskiren alone and in combination with other antihypertensive drug classes, further support its use in the control of high blood pressure.

Aliskiren is the first in a new class of potent, orally effective renin inhibitors. It acts by targeting the renin-angiotensin system (RAS) at the first and rate-limiting step. Although aliskiren increases renin production, the renin produced is inhibited and its capacity to form angiotensin I, as measured by plasma renin activity (PRA), is reduced. By contrast, ACE inhibitors, ARBs, and thiazide diuretics all increase plasma renin concentration and PRA, producing angiotensin I, which
is then available for conversion to angiotensin II. In addition, renin inhibitors do not affect kinin metabolism and hence would not be expected to cause dry cough or angioneurotic edema, both characteristic side effects of ACE inhibitors.

Since 2002, aliskiren has been developed solely by Novartis (Basel, Switzerland). The first regulatory submission for aliskiren as monotherapy and in combination therapy in the treatment of hypertension was made in the United States in April, and in September the European Medicines Agency announced that it had accepted a regulatory submission for aliskiren for the same indications. If this drug is accepted, it will be the first of the direct renin inhibitors, which are expected to be the first new class of antihypertensive medications to become available for a decade. The trade name pending approval for aliskiren is Rasilez.

First clinical data on aliskiren were presented earlier this year at the annual meetings of the American Society of Hypertension and the European Society of Hypertension. The data presented at the WCC show that once-daily aliskiren, used either as monotherapy or in combination therapy, provides consistent and sustained blood pressure lowering over 12 months of treatment, providing sustained 24-hour blood pressure control, with no rebound high blood pressure after discontinuation of therapy. Additive blood pressure reductions were seen when aliskiren was added to the diuretic hydrochlorothiazide (HCTZ) or to the ACE inhibitor ramipril. In combination with amlodipine, aliskiren provided the same efficacy, with a lower incidence of edema, than a higher dose of amlodipine. Aliskiren up to doses of 300 mg showed placebo-like tolerability, with no ACE-related cough and evidence of a lower incidence of cough when used in combination with an ACE inhibitor than when an ACE inhibitor was used alone.

Aliskiren plus HCTZ. The results of a 12-month, open-label study presented jointly by Domenic Sica, MD (Medical College of Virginia Commonwealth University, Richmond, Virginia) and James Pool, MD (Baylor College of Medicine, Houston, Texas) revealed that aliskiren alone and in combination with HCTZ reduced blood pressure effectively and maintained its blood pressure-lowering effect over 1 year of therapy. The study concluded with a final 1-month, randomized, placebo-controlled withdrawal period in which patients were randomized to continue aliskiren or placebo during a 4-week double-blind withdrawal phase.

At the end of the open-label treatment period, reductions in DBP and SBP in the aliskiren monotherapy groups and the aliskiren/HCTZ groups were similar. During the withdrawal period, patients on placebo had a gradual increase in mean sitting blood pressure that appeared to plateau after 3 weeks. In the patients who remained on aliskiren, blood pressure reductions were maintained at levels similar to those seen at Month 11. At the end of the withdrawal period, there was a statistically significant difference in blood pressure between the aliskiren and placebo groups (5.99/3.87 mm Hg; P < .0001).

Twenty-four-hour ABPM showed a clear separation between aliskiren and placebo at most hourly time points, showing that reductions in blood pressure with aliskiren were sustained throughout the 24-hour dosing period, and the investigators noted that "the blood pressure response numbers are quite comparable to monotherapy with an ACE inhibitor or an ARB."

PRA, measured in a subset of patients, showed similar sustained reductions from baseline with aliskiren as monotherapy and in combination therapy. These reductions in PRA were maintained during long-term (12 months) treatment for monotherapy and combination therapy, indicating that aliskiren effectively suppresses PRA even when used in combination with drugs that increase PRA. Renin concentration increased in patients taking aliskiren during the open-label treatment period, but was more marked in the patients on aliskiren HCTZ. During the withdrawal period, PRA remained suppressed in patients who continued on aliskiren despite renin levels that remained above baseline levels. In the patients who switched to placebo, PRA remained > 50% below baseline levels even after 4 weeks, although renin concentration returned to almost baseline levels by study endpoint, suggesting continued renin inhibition with aliskiren beyond the drug's plasma half-life.

Dr. Sica believes that aliskiren may be one of the first drugs with an effect related to tissue compartmentalization and not to plasma levels. "That is new and very novel and may speak well for issues of end-organ protection," he predicted. "We still have a lot to learn about the drug, but we have good reasons to believe that it may be different," he said.

There was no evidence of dose-dependent side effects during open-label treatment with aliskiren alone or with HCTZ. During the withdrawal period, adverse rates were similar in patients on aliskiren (15.9%) and placebo (14.7%).

Aliskiren plus amlodipine or ramipril. Another study showed that adding aliskiren 150 mg to amlodipine 5 mg provides significant additional blood pressure lowering without increasing the incidence of the edema associated with doubling the amlodipine dose. In the study reported by Mark Munger, PharmD (College of Pharmacy, University of Utah, Salt Lake City),[5] aliskiren alone or in combination with amlodipine produced significantly greater reductions in mean sitting DBP and SBP between baseline and study endpoint (Week 6), the primary efficacy measure of the study, than amlodipine 5 mg alone ($P < .0001$).

The results of a substudy that compared the effects of 8 weeks of treatment with aliskiren, ramipril, or both drugs in combination were presented by Charles Kilo, MD (Washington University School of Medicine, St Louis).[6] In general, RAS inhibition is beneficial in the management of hypertension in patients with diabetes, but monotherapy is often insufficient to achieve the stringent blood pressure control required in this population, Dr. Kilo noted. In 256 adult male or female patients with type 1 or 2 diabetes and hypertension, aliskiren 300 mg was superior to ramipril 10 mg in lowering mean sitting SBP, and noninferior in lowering mean sitting DBP. The aliskiren/ramipril combination provided significant additional blood pressure lowering, however.

Plasma renin concentrations increased significantly in all treatment groups compared with baseline, with a greater increase in the aliskiren group (115%) than in the ramipril group (68%), and the largest increase seen with combination therapy (315%). However, while PRA increased by 111% in the ramipril group, it was reduced by 68% in the aliskiren group. In combination therapy, aliskiren counteracted the ramipril-induced increase in PRA, leading to an overall reduction of 44%. The combination of aliskiren and ramipril was well tolerated.

Pooled aliskiren results. Matthew R. Weir, MD (University of Maryland School of Medicine, Baltimore), presented the results of an analysis of pooled data from 7 randomized, double-blind, multicenter studies with aliskiren as monotherapy or in combination.[7] The results of the analysis showed that aliskiren monotherapy effectively and dose-dependently lowers blood pressure, with effects independent of age or gender and placebo-like tolerability. The 150-mg and 300-mg doses of aliskiren consistently provided additional blood pressure reductions when added to other antihypertensive agents without compromising tolerability.

Addition of aliskiren 150-300 mg to other classes of antihypertensive drugs (diuretic, ACE inhibitor, ARB, or CCB) was associated with additional, mainly significant reductions in blood pressure. No substantial additional blood pressure-lowering effect was seen with aliskiren added to valsartan, but this may have been due to the lower numbers in this study, and further studies are needed to determine the effect of aliskiren in combination with ARBs, Dr. Weir noted.

In placebo-controlled studies of aliskiren, tolerability of doses up to 300 mg once daily did not differ significantly from that of placebo. The most common adverse events, reported by ≥ 2% of patients, were headache, nasopharyngitis, and diarrhea. Headache showed a trend toward reduction in incidence with increase in dose. The incidence of diarrhea with aliskiren was significantly higher than with placebo overall ($P < .05$), due mainly to the effect of the 600-mg dose (9.5%; $P < .0001$ vs placebo) that was not seen with the 150- or 300-mg doses. Tolerability was not affected by addition of other agents to aliskiren. Overall, > 95% of adverse events with aliskiren were mild or moderate in severity, and most were considered not to be related to study treatment.

An ongoing clinical development program with aliskiren includes 2 key studies, scheduled to begin in 2007, that aim to define the role of direct renin inhibition in primary and secondary prevention. Aliskiren in Visceral Obesity AT risk patients Outcomes Research (AVIATOR) is a prehypertension study designed to determine whether aliskiren delays the time to first major cardiovascular event in approximately 15,000 high-risk subjects. The ALiskiren Trial in Type 2 Diabetic nephropathy (ALTITUDE) will enroll approximately 6000 subjects to determine whether aliskiren delays the time to diabetic complications. Both of these studies are scheduled to report results between 2011 and 2013. Two other studies will examine the effects of aliskiren on surrogate markers of target organ damage. Aliskiren is also in phase 2 trials to determine its role in the treatment of heart failure.

Aliskiren is believed to have a 5-year lead over the next generation of renin inhibitors being developed by the pharmaceutical industry. Other companies with
renin inhibitors in phase 1 clinical trials include Speedel (Basel, Switzerland) with SPP635, and a compound being developed jointly by Actelion (Allschwil, Switzerland) and Merck (Whitehouse Station, New Jersey). Other companies have renin inhibitors in preclinical studies.

**Role for Phosphodiesterase Type 5 Inhibition in Long-term Treatment of Hypertension**

The results of the first controlled clinical trial of regular phosphodiesterase type 5 (PDE5) inhibitor therapy as a long-term treatment of hypertension suggest that these drugs effectively reduce blood pressure and that further studies are warranted to evaluate their use in clinical practice. However, the longer-acting PDE5 inhibitors or, alternatively, extended-release preparations of existing drugs with a shorter duration of action, would be more suitable for chronic use, say the UK researchers who carried out the trial. Their study, which was supported by Pfizer United Kingdom, is published in the October issue of *Hypertension*[^10].

PDE5 inhibitors are widely available for the treatment of erectile dysfunction. The observed effects of PDE5 inhibitor therapy on endogenous nitric oxide (NO)-mediated effects, such as vascular smooth muscle relaxation, led to the suggestion that PDE5 inhibitor therapy might be suitable for the chronic treatment of hypertension. Previous studies with the PDE5 inhibitor sildenafil in hypertensive patients showed acute reductions in blood pressure, but the patients in these studies were taking other antihypertensive drugs. No study had previously investigated sildenafil alone as antihypertensive therapy.

Researchers at the University of Edinburgh, Scotland, led by Prof. David J. Webb, MD (Centre for Cardiovascular Science),[^10] carried out a randomized, double-blind, 2-way crossover study in 25 untreated hypertensive subjects identified from primary care and hospital hypertension clinics. The patients took oral doses of sildenafil 50 mg or matched placebo 3 times daily (morning, early afternoon, and evening) for 16 days. There was a washout period of ≥ 6 days between treatments. The effects on ambulatory blood pressure, clinic blood pressure, arterial wave reflection, carotid-femoral pulse wave velocity, and brachial artery flow-mediated dilatation were assessed during each study period.

Three subjects were withdrawn because of adverse effects (2 on sildenafil and 1 taking placebo), so that data were available for analysis from the remaining 22 subjects. The subjects taking sildenafil complained of severe headache and back pain, but the main adverse effects of sildenafil, which were generally transient and rated as mild to moderate in severity, were dyspepsia, headache, and myalgia.

Sildenafil significantly reduced systolic and diastolic ambulatory 24-hour daytime and nighttime blood pressures from baseline compared with placebo. The reduction from baseline in average daytime blood pressure with sildenafil compared with placebo was SBP 8 mm Hg vs 2 mm Hg (P < .01), and DBP 6 mm Hg DBP vs 0 mm Hg (P < .01). Neither sildenafil nor placebo affected blood pressure variability.

Sildenafil reduced clinic blood pressure acutely (1 hour after administration) and after 16 days of regular administration. The respective reductions from baseline to 1 hour after drug administration on Day 16 were SBP 5 mm Hg vs 4 mm Hg (P < .01) and DBP 5 mm Hg vs 2 mm Hg (P <.01). These reductions are similar to the effects of commonly used antihypertensive drugs when given as monotherapy in hypertension, the researchers note. Sildenafil did not affect clinic pulse pressure to heart rate, acutely or chronically. Sildenafil reduced blood pressure acutely (1 hour after administration) and after 16 days of regular administration.

Prof. Webb and his colleagues noted that although there was a persistent hypotensive effect of sildenafil over 16 days, there was some attenuation of the acute effect. This may be the result of neurohormonal counter-regulatory mechanisms such as stimulation of the renin-angiotensin system after the initial vasodilation-mediated reduction in blood pressure, they suggest. On Day 16 of treatment, clinic blood pressure was higher before the administration of sildenafil than at 1 hour afterward. Although average nighttime blood pressure was reduced, the researchers say, this suggests that the overnight dose interval allowed the antihypertensive effect to begin to wane. This may have clinical relevance given the importance of the early-morning surge in blood pressure as a trigger of cardiovascular events, they note. A longer-acting PDE5 inhibitor, such as tadalafil, or a modified-release preparation of sildenafil (not currently available) might overcome this problem by providing a more stable steady-state plasma concentration. It might also provide a greater cumulative reduction in

[^10]: New Definitions and New Classes of Antihypertensive Drugs Show Promise

blood pressure, they suggest.

Compared with baseline, sildenafil, but not placebo, reduced arterial wave reflection both acutely and after chronic treatment, but the chronic change in arterial wave reflection was not statistically different from the chronic change with placebo. Sildenafil did not affect pulse wave velocity or flow-mediated dilatation, indicating that it did not modulate endothelium-dependent vasomotion acutely or after chronic treatment. Since flow-mediated dilatation is largely NO mediated, "it would seem logical" that sildenafil, by preserving NO-stimulated cGMP, would improve it, the researchers say. They suggest that the lack of effect in this study might be explained by the lesser contribution of NO to shear stress-induced vasodilatation at the brachial artery in hypertensive subjects.

Most antihypertensive drug classes do not consistently improve flow-mediated dilatation and yet "with the exception of beta-blockers, these drugs are substantially equivalent in reducing cardiovascular events," they say. "Therefore, the lack of effect of sildenafil on flow-mediated dilatation should not, in itself, detract from its potential as an antihypertensive in clinical practice."

Prof. Webb and coauthors suggest that studies comparing the efficacy and tolerability of PDE5 inhibitors with established antihypertensives "would help to determine their place in clinical practice." They believe that a potentially valuable indication for these drugs would be in men with erectile dysfunction. "It would be necessary to demonstrate that the effect of PDE5 inhibitors on erectile function is maintained in the long term with the regular dosing pattern that would be required for the treatment of hypertension," they stress.

Comment

In an accompanying editorial, Prof. Stefano Taddei, MD, and Prof. Lorenzo Ghiadoni, MD (University of Pisa, Italy),[11] conclude that the Edinburgh study indicates that "PDE5 inhibition might be a valid option to reduce blood pressure in hypertensive patients." "Obviously this is only the beginning of the story, and a more complete development of sildenafil or other PDE5 inhibitors as antihypertensive drugs is needed," they say. "Important issues to be addressed include: the use of slow-release formulations or compounds with long half-life to assure a homogenous blood pressure-lowering effect lasting 24 h; the demonstration of the safety of these drugs during long-term administration; and the evaluation of interactions with antihypertensive and nonantihypertensive drugs."

Prof. Taddei and Prof. Ghiadoni call for studies to identify the mechanism responsible for "the lack of sympathetic activation and tachycardia evoked by sildenafil-induced blood pressure reduction." Additional areas of investigation should include confirmation that sildenafil has no specific effect on arterial stiffness and further studies on the effects of PDE5 inhibitors on endothelial dysfunction, even though "it is possible to state that sildenafil does not improve conduit artery endothelial function in essential hypertensive patients."

"A final and crucial aspect is the effect of PDE5 on target organ damage," the authors stress. Although the results of the study do not support specific effects on conduit artery function, prolonged treatment might give different results, especially on vascular structural changes, they suggest. "In addition, the effect of PDE5 inhibition on other major determinants of hypertensive organ damage, including left ventricular hypertrophy and microalbuminuria, needs to be assessed. If the story is to have a positive end, PDE5 inhibitors may be a useful adjunctive drug class for the pharmacological treatment of essential hypertension and improved blood pressure control in the general population," they conclude.

Significant Association Reported Between Diagnosis of Breast Cancer and Hypertension Treated With Diuretics

There is a modest but significant association between treated hypertension and breast cancer risk in women aged 50-75 years, according to the results of a new US study published in the *Journal of Human Hypertension*. The study showed that this association was strongest in women who were diagnosed with hypertension at a younger age (< 55 years), and regular diuretic use for treatment of hypertension or other indications was also significantly associated with
breast cancer risk. Further analysis suggested that the breast cancer risk associated with treated hypertension was confined to women with a BMI ≥25 kg/m². "These results have implications for implementing cancer preventive strategies for those with hypertension, using diuretics, and those who are overweight," say lead investigator Joan A Largent, PhD, MPH, and her colleagues at the University of California, Irvine.

For the National Cancer Institute-sponsored study, Dr Largent's group identified 523 breast cancer cases from the population-based cancer registry of Cancer Surveillance Program of Orange County, California. These patients, all between the ages of 50 and 75 years, were identified within 6 months of diagnosis between March 1, 1994, and February 28, 1995. A total of 131 female controls aged 50-75 years with no history of cancer were randomly selected from Orange County residents using random-digit-dialing between December 1997 and February 1999. All the study participants completed a self-administered questionnaire asking for information about history of hypertension, antihypertensive medication use ("water pills," "reserpine," or "other blood pressure medication"), and risk factors.

Analysis adjusting for age, BMI, diabetes, smoking, alcohol use, menopausal status, family history of breast or ovarian cancer, age at first full-term pregnancy and education, showed that history of treated hypertension was associated with a significantly increased risk of breast cancer (OR, 1.77; 95% confidence interval [95% CI], 1.04-3.03). This risk increased as age at hypertension diagnosis decreased (P for trend = .02).

Regular diuretic use was also associated with elevated breast cancer risk (OR, 1.79; 95% CI, 1.07-3.01), this risk increasing with duration of diuretic use (P for trend, < .01). By contrast, use of reserpine or "other blood pressure medications" was not significantly associated with breast cancer risk.

The association between treated hypertension and breast cancer risk appeared to be stronger in younger women (age 50-64 years) and significant only in women with BMI ≥25 kg/m² (OR, 2.30; 95% CI, 1.12-4.71), but not women with normal weight.

An association between breast cancer and hypertension has been reported previously. Several mechanisms have been proposed for this association. "Breast cancer and hypertension may share common pathophysiological pathways including those involved in inflammation and hormone synthesis and metabolism," say Dr. Largent and her colleagues -- "perhaps an environment of chronic inflammation, induced by both hypertension and breast cancer in these women."

They also note that steroid hormone factors are involved in the progression of both conditions. Hypertension itself may provide an environment that supports the development of cancer by inhibiting apoptosis over the long term, thereby increasing cancer risk. It cannot be ruled out that the effect of diuretic use in this study was owing to the underlying condition of hypertension, or vice versa, the researchers point out.

Comment

In an accompanying commentary, Prof Gregory YH Lip, MD and Patrick KY Goon, MRCS (City Hospital, University of Birmingham, UK)[13] and Franz H Messerli, MD (St. Luke's-Roosevelt Hospital, New York, NY) say that in the light of current evidence, Dr. Largent's study "raises questions but does not deliver firm answers. Although interesting, their findings are largely contrary to the bulk of published evidence, possibly explained away by bias alone and, as such, must be viewed with a healthy degree of skepticism until such time as better designed trials become available." They caution against reaching conclusions too quickly. "In our opinion," they conclude, "the link between breast cancer, hypertension and diuretics remains unexplained, largely unqualified and clinically insignificant so as to warrant 'no change' in current treatment guidelines."

Implantable Device for Treatment of Resistant Hypertension Progresses in Clinical Development

The first implantable device being developed to treat patients with refractory hypertension has been given the go-ahead for a pivotal phase 3 clinical trial in the United States. CVRx, Inc., a private company based in Minneapolis (Minnesota), announced in October that it had received a conditional investigational device exemption (IDE) approval from the US Food and Drug Administration (FDA) to begin a US pivotal clinical trial that will evaluate the safety and
effectiveness of the Rheos Baroreflex Hypertension Therapy (Rheos BHT) System.\textsuperscript{14} Data from this clinical trial are intended to support the Pre-Market Approval (PMA) application for the Rheos System to the FDA.

The Rheos BHT System provides a "physiological rational approach" to reducing high blood pressure by allowing the brain to direct the body's control mechanisms. It works by electrically activating the baroreflex, the system that regulates blood pressure. Signals are sent to the central nervous system that are interpreted as an excessive rise in blood pressure, and this perceived rise is counteracted by a reduction in heart rate and decreased efferent outflow. The Rheos BHT System consists of the pulse generator, an iPod-sized device that is surgically implanted under the skin, and 2 electrodes bilaterally implanted circumferentially around the carotid arteries at the level of the carotid sinus. Two leads, which run under the skin, conduct activation energy from the implantable pulse generator to the left and right carotid sinus, and a programmer system allows noninvasive communication with the pulse generator. The Rheos BHT System is intended for use in patients who cannot control their blood pressure with medications and lifestyle modifications (refractory or resistant hypertension). The device is under clinical investigation at this time and is not yet approved for commercial sale.

"The Rheos System represents a fundamentally new approach to therapeutic intervention for resistant hypertension," said the clinical trial's principal investigator, Thomas G Pickering, MD, DPhil (Columbia University Medical Center - Presbyterian Hospital, New York). "This pivotal study will help us further understand the potential role of this device in treating patients with difficult-to-manage high blood pressure. Reducing high blood pressure can help prevent serious heart and kidney disease, stroke and death."

Sponsored by CVRx, the blinded study is a prospective, randomized, multicenter clinical trial that will be conducted at up to 40 medical sites. The study seeks to determine the safety and effectiveness of the Rheos BHT System when used in drug-resistant hypertensive patients. To be enrolled in the trial, patients need to be resistant to treatment with at least 3 antihypertensive medications, including a diuretic, and have an SBP $\geq$ 160 mm Hg.

European and US feasibility clinical trials are evaluating the Rheos System in hypertensive patients. Preliminary results from the European trial, the Device Based Therapy of Hypertension (DEBuT-HT) study, were presented by Prof. Peter W de Leeuw, MD, PhD (University Hospital Maastricht, The Netherlands) at the recent European Society of Hypertension meeting in Madrid.\textsuperscript{15} The aim of the DEBuT-HT trial was to show a 10-mm Hg decrease in SBP from baseline after 3 months of incrementally optimized therapy and to demonstrate the safety of the system. Patient enrollment started in 2004 at 4 centers. All patients had SBP $\geq$ 160 mm Hg, DBP $\geq$ 90 mm Hg, and had had $\geq$ 2 months of therapy with a diuretic and $\geq$ 2 other antihypertensive medications.

At the prespecified 3-month follow-up, the first 16 patients (8 men and 8 women) showed significant reductions of 29 mm Hg in SBP and 15 mm Hg DBP ($P < .001$ for both). Heart rate was also reduced. Data available for 8 and 12 months indicated a similar trend with a background of changing medications. No unanticipated adverse device effects or lead or pulse generator failures were seen with the system. One infection required explantation. Other serious system and/or procedure-related events included transient intraoperative bradycardia, postoperative tongue paresis, and delayed wound healing (culture negative). There was no evidence of carotid artery stenosis.

Initial results of the US study will be presented at the American Heart Association annual meeting in Chicago in November 2006.

**Action on Hypertension in China as Prevalence Rises and Market for Antihypertensive Drugs Increases**

A project that will train 20,000 community doctors to help patients with hypertension has been launched in China, according to a spokesperson from the Ministry of Health. The Ministry says that at least 160 million people in China have hypertension, which equates to 12.3% of the total population and an increase of 31% over the past decade. Adoption of a more Western lifestyle, including diet and (lack of) exercise, and increased urbanization have been blamed for this increase. Despite the increase in the number of cases, public awareness of hypertension and its treatment in China remain low, a health official said. Only 6.1% of hypertensive patients are monitored by doctors. Many patients do not have their blood pressure monitored or have regular contact
The 2-year cooperative project was launched jointly by the health ministry and Beijing Novartis Pharma Ltd, the China office of Novartis (Basel, Switzerland). The project will promote public awareness and control of hypertension "and the company's hypertension medicines," the announcement said. It aims to monitor 1 million hypertensive patients and raise the monitoring rate to 60% patients nationwide.

Ten hospitals in cities such as Beijing and Shanghai were selected to organize lecture teams that will conduct training in 70 cities across the country in 2006 and 2007. The trainees are mainly doctors in hospitals and medical workers in community health service centers, said Huang Qiongli, Director of the development center for medical science and technology under the ministry.

A new US report\cite{16} confirms that China has identified hypertension as a primary target in its first long-term national plan for chronic disease control and prevention. "This urban reform toward community care has the potential to significantly boost disease awareness in cities. Access to basic medical care in rural areas should also rise as a new rural cooperative medical scheme expands and provides wider access to diagnostic techniques and treatments with cheaper Western drugs. Diagnosis rates for hypertension will rise from 33% in 2005 to 41% in 2010, the report says.

The market for antihypertensive drugs in China will almost double from $440 million in 2005 to more than $800 million US dollars by 2010, the report predicts. It says that the increase will be driven by an increase in the number of people with hypertension. Calcium channel blockers will remain the most widely prescribed antihypertension medications in China, the report's authors believe.

References


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