

## **SYSTOLIC HYPERTENSION BACKGROUNDER**

### **Understanding Blood Pressure**

High blood pressure (hypertension) is a serious and extremely common medical condition affecting approximately one in four adults. Left untreated, hypertension can cause stroke, heart attack, heart failure, kidney damage, dementia, and blindness. Blood pressure is typically recorded as two numbers – the systolic pressure over the diastolic pressure. The systolic pressure, or the upper number, is the pressure of blood in the vessels when the heart contracts. Diastolic pressure, or the lower number, is the pressure of the blood between heartbeats when the heart is at rest and is refilling. According to the most recent guidelines issued in 2003 by the National Heart, Lung, and Blood Institute (NHLBI), optimal blood pressure is less than 120/80 mm Hg. Hypertension is defined as a systolic blood pressure of 140 mm Hg or greater, or a diastolic blood pressure of 90 mm Hg or greater. In most people, systolic blood pressure increases steadily with age, in conjunction with increased stiffness of large arteries, and the prevalence of cardiac and vascular disease, while the diastolic blood pressure increases until about age 55 and then decreases.<sup>1</sup>

### **A Paradigm Shift**

As recently as 1997, physicians relied on diastolic blood pressure to diagnose hypertension and assess cardiovascular risks in patients of all ages. However, major clinical studies, (including the Framingham Heart Study, the Cardiovascular Health Study, and the National Health and Nutrition Examination Survey, (NHANES III), have produced a paradigm shift in the national recommendations for the diagnosis and treatment of hypertension. By the year 2000, key scientific evidence from these studies had emerged proving that **systolic hypertension** (an elevated, systolic pressure), with an estimated prevalence of 15 to 20 million people in the U.S. alone, is the most common form of hypertension and is present in more than 80 percent of people with high blood pressure age 50 and over.<sup>1</sup> According to the current recommendations by the NHLBI, “systolic blood pressure is the key determinant for assessing the presence and severity of high blood pressure for middle-aged and older adults.”

Among the aged, measurement of systolic – and not diastolic – blood pressure better identifies people with high blood pressure and also those who are at increased risk of developing cardiovascular disease.<sup>2</sup> However, according to the American Heart Association, systolic hypertension is the least likely form of high blood pressure to receive treatment. To date, no approved drug for high blood pressure directly targets the underlying age-related vascular stiffening that results in systolic hypertension, and thus this condition represents a major unmet medical need. Currently available blood pressure medicines such as beta-blockers, diuretics and ACE inhibitors typically lower both systolic and diastolic pressures. Unfortunately, patients receiving these treatments for systolic hypertension have been shown to be at risk of experiencing hypotension or too low a diastolic pressure.

### **Joint National Committee (JNC) Hypertension Guidelines Issued in May 2003**

Warranted by results of recent major clinical studies, the NHLBI recently mandated the publication of new hypertension guidelines (JNC VII, May 2003). These guidelines, issued by the Joint National Committee (JNC) of the National High Blood Pressure Education Program, a coalition administered by the NHLBI, are intended to increase awareness, prevention, and treatment of hypertension among clinicians. JNC VII updates the earlier JNC VI guidelines (1997) and emphasizes systolic hypertension as “a more important [cardiovascular disease] risk factor than diastolic BP [blood pressure]” in patients over 50, and urges physicians to focus on treating systolic pressure to reach a goal level lower than 140 mm Hg. The JNC VII guidelines also emphasize that once systolic pressure reaches goal levels, a reduction in diastolic blood pressure to target levels (lower than 90 mm Hg) will ensue.

### **Treating the Cause of Systolic Hypertension**

In response to the emerging evidence concerning the risks associated with systolic hypertension over the last several years, Alteon Inc. (AMEX: ALT), is developing a new oral medicine, ALT-711, to treat the underlying cause of systolic hypertension. As arteries lose their elasticity through the build up of glucose/protein chemical bonds known as A.G.E. crosslinks, the pressure required to push blood through blood vessels increases, placing greater strain on the heart. ALT-711 breaks down the rigid glucose/protein chemical bonds that cause stiffening of the vessels, organs, and tissues. Currently in late-stage clinical development, ALT-711 has demonstrated efficacy against systolic hypertension as well as other cardiovascular conditions.

ALT-711 is the first in a new class of medicines being developed by Alteon to reverse or slow down diseases of aging and complications of diabetes. These compounds have an impact on a fundamental pathological process caused by protein-glucose complexes called Advanced Glycation End-products (A.G.E.s). The formation and crosslinking of A.G.E.s lead to a loss of flexibility and function in body tissues, organs and vessels and have been shown to be a causative factor in many age-related diseases and diabetic complications. Alteon is initially developing therapies for cardiovascular and kidney diseases in older or diabetic individuals.

For further information on ALT-711 clinical findings, systolic hypertension and A.G.E. Crosslink Breakers, please contact Susan Pietropaolo at 201-934-5000 or visit the Alteon Inc. website at [www.alteon.com](http://www.alteon.com).

#### References:

1. Izzo Jr., Joseph L. et al, Clinical Advisory Statement: “Importance of systolic blood pressure in older Americans,” *Hypertension: Journal of the American Heart Association*, May 2000
2. National Institute on Aging

# THE EMERGENCE OF SYSTOLIC HYPERTENSION AS A LEADING RISK FACTOR FOR CARDIOVASCULAR DISEASE AND MORTALITY

## TIMELINE

**1997:** The JNC VI guidelines issued by the Joint National Committee (JNC) of the National High Blood Pressure Education Program noted the importance of systolic blood pressure to cardiovascular risk. The guidelines recommended using both systolic and diastolic blood pressures for diagnosis and treatment at all ages. The guidelines also recommended diuretics as a first-line treatment for systolic hypertension and the need to individualize treatment, along with recommended values of 140/90 mm Hg. Only 1 in 4 Americans with hypertension fell below JNC VI recommended values.

**1998-2000:** Publications from the National Heart Lung and Blood Institutes's (NHLBI) long-term Framingham Heart Study reported new evidence of a relationship between systolic hypertension and mortality and new statistics on systolic blood pressure as a diagnostic tool. For example, one study found systolic blood pressure alone correctly identified 91 percent of those who may need antihypertensive therapy, while diastolic blood pressure alone correctly identified only 22 percent of them. The study involved nearly 5,000 persons.

**2000:** Enlightened by results of the major clinical studies, the NHLBI and its National High Blood Pressure Education Program initiated a campaign to raise awareness of the dangers of systolic hypertension, and produced a clinical advisory recommending "a major paradigm shift in urging that systolic [blood pressure] become the major criterion for diagnosis, staging, and therapeutic management of hypertension, particularly in middle-aged and older Americans."<sup>1</sup> The advisory noted that hypertension control rates are poorest in older people, primarily as a result of inadequate systolic [blood pressure] control, and highlighted that controlling systolic hypertension significantly reduced heart attack, heart failure, and stroke, and recommended reducing systolic blood pressure to less than 140 mm Hg.

**2001:** An analysis of the National Health and Nutrition Examination Survey, (NHANES) III, (conducted by the National Center for Health Statistics, Centers for Disease Control and Prevention) of 19,661 adults found systolic hypertension to be the dominant form of uncontrolled high blood pressure in people age 50 and over, occurring in more than 80 percent of individuals in this age group who have high blood pressure.<sup>2</sup>

**2002:** "Systolic hypertension emerges as the single most important modifiable risk factor at older age," as written in a chapter on geriatric cardiology in ACCSAP V, an award-winning self-assessment program published by the American College of Cardiology Foundation.

A major international study comparing older patients with diastolic hypertension to those with normal diastolic pressures and systolic hypertension determined that the greater the gap between systolic and diastolic pressures, the more extensive the atherosclerosis in carotid arteries and enlargement of the left ventricle. Even in people with lower average blood pressures, higher pulse pressures (the difference between systolic and diastolic pressures) were associated with these cardiovascular issues. The researchers noted that while current blood pressure therapies are beneficial, they only treat diastolic hypertension and pointed to a need for new blood pressure medications "that will be able to decrease the systolic pressure without changing the diastolic pressure."<sup>3</sup>

The National Heart, Lung and Blood Institute (NHLBI), the American Heart Association (AHA) and the American College of Cardiology (ACC) call for drugs that specifically decrease systolic pressure without reducing or over treating diastolic pressure to achieve optimal control of hypertension.<sup>3</sup>

**2003:** The Joint National Committee of the NHLBI's National High Blood Pressure Education Program issued the most recent guidelines, JNC VII in May. The guidelines were written in response to new findings from several major clinical studies including the Framingham Heart Study, the Cardiovascular Health Study, and the National Health and Nutrition Examination Survey, (NHANES) III. JNC VII points to systolic hypertension as a more important cardiovascular disease risk than diastolic hypertension and calls for a new focus on its treatment. The guidelines also introduce a new class of hypertension, in adults 18 and older, termed "prehypertension" and classified by lower systolic and diastolic pressures (120-130/80-90) than hypertension.

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### References:

1. Izzo Jr., Joseph L. et al, Clinical Advisory Statement: "Importance of systolic blood pressure in older Americans", Hypertension: Journal of the American Heart Association, May 2000
2. Franklin, M.D, Stanley S. "Top number too high in blood pressures of people over age fifty", Hypertension: Journal of the American Heart Association, March 2001
3. Pini et al, Journal of the American College of Cardiology, October, 2002.