[Article 1 – Abstract]

***Background***

The prevention of hypertension with the angiotensin-converting enzyme inhibitor ramipril in patients with high-normal blood pressure study addresses the issue of whether progression to manifest hypertension in patients with high-normal blood pressure can be prevented with treatment.

***Methods***

A total of 1008 participants with high-normal office blood pressure were randomized to ramipril treatment group (n ***=*** 505) and a control group (n = 503). The patients were followed up for 3 years. Primary endpoint was to prevent or delay the progression to manifest hypertension. Secondary endpoints were reduction in the incidence of cerebrovascular and cardiovascular events, as well as the development of hypertension as defined by ambulatory blood pressure monitoring.

***Findings*** One hundred and fifty-five patients (30.7%) in the ramipril group, and 216 (42.9%) in the control group reached the primary endpoint (relative risk reduction 34.4%, *P****=*** 0.0001). Ramipril also proved to be more effective in reducing the incidence of manifest office hypertension in patients with baseline ambulatory blood pressure monitoring high-normal blood pressure. The incidence of cerebrovascular and cardiovascular events showed no statistically significant differences between the two groups. Cough was more frequent in the ramipril group (4.8 vs. 0.4%).

***Interpretation*** There is now good clinical evidence that patients with high-normal blood pressure (prehypertension) are more likely to progress to manifest hypertension than patients with optimal or normal blood pressure. Additional ambulatory blood pressure monitoring

seems to be essential to achieve correct diagnosis. Treatment of patients with high-normal office blood pressure with the angiotensin-converting enzyme inhibitor was well tolerated, and significantly reduced the risk of progression to manifest hypertension

[Article 1 – Conclusion]

The results of the TROPHY and the PHARAO studies are the first two clinical trials confirming that treatment of prehypertensive patients, or these with high-normal BP, with candesartan or ramipril as monotherapy reduced the incidence of manifest hypertension, PHARAO shows the importance of including ABPM to achieve correct diagnosis and classification of patients with prehypertension. Additional larger and longer-term trials in participants with high-normal BP levels arc urgently needed to evaluate whether nonpharmacological or pharmacological treatment will positively affect cardiovascular risk factor and clinical outcomes.

[Article 2]

**Potential health impact and cost-effectiveness of drug therapy for prehypertension.**

Abstract

*Background:*

Studies have reported that pharmacologic interventions with candesartan or ramipril could reduce the risk of hypertension among prehypertensive subjects free of clinical cardiovascular disease (CVD), however, the cost-effectiveness and long-term cardiovascular risk of drug treatment among these population is unclear.

(…)

*Results:*

Compared with placebo, drug treatment resulted in delaying the development of hypertension by nearly 12years and reducing the absolute incidence of hypertension by 32.01% over lifetime. The cumulative incidence of coronary heart disease, stroke and heart failure were reduced and survival was improved from 28.46 to 28.80 years. (…)

*Conclusion:*

Drug treatment for prehypertension may help stem the current epidemic of hypertension among Chinese adults free of CVD, which may in turn reduce CVD complications and potentially be cost effective.

[Article 3]

**Prehypertension: Underlying pathology and therapeutic options**

**Abstract**

Prehypertension (PHTN) is a global major health risk that subjects individuals to double the risk of cardiovascular disease (CVD) independent of progression to overt hypertension. Its prevalence rate varies considerably from country to country ranging between 21.9% and 52%.

(…) Leading clinical guidelines suggest using dietary and lifestyle modifications as a first line interventional strategy to curb the progress of PHTN; however, other clinically respected views call for using drugs. This review provides an overview of the potential pathophysiological processes associated with PHTN, abridges current intervention strategies and suggests investigating the value of using the “Polypill” in prehypertensive subjects to ascertain its potential in delaying (or preventing) CVD associated with raised blood pressure in the presence of other risk factors.

[Article 4]

**Prehypertension**

A meta-analysis of the epidemiology, risk factors, and predictors of progression.

*We investigated the prevalence and risk factors of prehypertension, as well as the predictors of progression from prehypertension to hypertension. To do this, we performed a systematic review and meta-analysis of cross-sectional and longitudinal studies, after unrestricted searches of PubMed and The Cochrane Library through September 2010. In addition, we reviewed references, major textbooks, and review articles. Pooled prevalence, standardized mean differences, and odds ratios were estimated by using a random-effects model.*

*Twenty-six articles met our inclusion criteria; these included 20 cross-sectional and 6 longitudinal studies, with a total sample of 250,741 individuals. The overall pooled prevalence of prehypertension was 36%. The pooled prevalence among males was higher than that among females (40% vs 33%).*

(…) *There were many modifiable risk factors associated with prehypertension, to which healthcare providers should pay more attention.* ***(Tex Heart Inst J 2011;38(6):643-52)***

[Article 5]

**Effectiveness of Chlorthalidone Plus Amiloride for the Prevention of Hypertension: The PREVER-Prevention Randomized Clinical Trial.**

*Background* – Prehypertension is associated with higher cardiovascular risk, target organ damage, and incidence of hypertension. The Prevention of Hypertension in Patients with PreHypertension (PREVER-Prevention) trial aimed to evaluate the efficacy and safety of a low-dose diuretic for the prevention of hypertension and end-organ damage.

(…)

*Conclusions* – A combination of low-dose chlorthalidone and amiloride effectively reduces the risk of incident hypertension and beneficially affects left ventricular mass in patients with prehypertension.

**In conclusion**, use of a fixed combination of low‐dose chlorthalidone and amiloride produced a substantial and highly significant reduction in the incidence of hypertension and a reduction in LVM in patients with prehypertension. The use of low‐dose diuretics in patients with prehypertension may be an effective option to reduce the burden of hypertension and its cardiovascular consequences.

[Article 6]

**Prehypertension is Associated With Abnormalities of Cardiac Structure and Function in the Atherosclerosis Risk in Communities Study.**

BACKGROUND

Prehypertension (blood pressure (BP) of 120-139 mm Hg systolic and/or 80-89 mm Hg diastolic) is highly prevalent and is associated with increased cardiovascular risk. Our goal was to investigate the extent to which prehypertension is associated with end-organ alterations in cardiac structure and function in a large biracial cohort of older men and women.

(…)

CONCLUSION

In the ARIC cohort at visit 5, prehypertension was associated with increased LV remodeling and impaired diastolic function, but not systolic function, suggesting that even mildly elevated BP within the normal range is associated with cardiac end-organ damage.

[Article 7]

**Prehypertension in disease-free adults: a marker for an adverse cardiometabolic risk profile.**

Cardiovascular disease (CVD) is the leading cause of death worldwide. Understandably, cardiometabolic risk assessment is an integral component of every adult health evaluation. Customary assessment measures are, however, inadequate: as two-thirds of sudden cardiac deaths occur in clinically healthy individuals. Novel indicators favoring early recognition of adverse cardiometabolic risk in disease-free adults are clearly needed. Clinically healthy disease-free adults with prehypertension (PreHTN: BP120-139/80-89 mm Hg) have an adverse cardiometabolic risk profile. A statistical analysis of disease-free adult NHANES participants was conducted from 1999 to 2006. Overall prevalence of PreHTN in disease-free adults was 36.3%. Prevalence was higher in men (P<0.001) increasing with age up to 70 years (P<0.001).

(…)

Prevalence of two or more unfavorable risk factors (other than high BP) was 30% higher in disease-free adults with PreHTN vs. desirable BP (prevalence ratio: 1.30; 95% CI: 1.22, 1.39). Detection of PreHTN (a precursor for subsequent HTN), during annual health maintenance in disease-free adults, (especially with one or more of the recognized CVD risk correlates), could become an early marker of adverse cardiometabolic risk profile. Clinical care designed to prevent progression from PreHTN to HTN (JNC 7 recommendation) may attenuate risk.

(…)

**Conclusion**

These data highlight PreHTN in disease-free healthy adults, a pre-cursor for subsequent hypertension, as an early correlate of an adverse cardiometabolic risk profile. Well-managed clinical interventions designed to prevent the progression from PreHTN to hypertension (based on JNC 7 recommendations) may modulate progression and attenuate risk.

[Article 8]

**Effect of antihypertensive therapy on incident stroke in cohorts with prehypertensive blood pressure levels**

**A meta-analysis of randomized controlled trials.**

***Background and purpose*** – Compared with normotensive individuals, there is a higher incidence of stroke in patients with hypertensive, as well as prehypertensive, blood pressure levels (ie, 120-139/80-89 mm Hg). Although several studies have shown that blood pressure reduction in hypertensive patients reduces the incidence of cardiovascular events, including stroke, it is still unknown whether treatment of prehypertensive blood pressure levels has a similar effect. We sought to determine whether reduction in blood pressure in the prehypertensive range reduces the incidence of stroke by performing a meta-analysis of randomized trials comparing an antihypertensive drug against placebo in cohorts with prehypertensive baseline blood pressure levels.

***Methods*** – Randomized controlled trials performed with the 95 different antihypertensive agents available in the market were identified using MEDLINE, returning a total of 2852 results. Exclusion criteria included: average blood pressure of ≥ 140/90 mm Hg at baseline, crossover studies, and lack of a control group receiving placebo.

(…)

***Conclusions*** – The risk of stroke is significantly reduced with antihypertensive therapy in cohorts with prehypertensive blood pressure levels. These findings can have important clinical implications.

(…)

**Conclusions**

This meta-analysis of over 70 000 patients shows that the risk of incident strokes is significantly reduced with antihypertensive therapy in cohorts with baseline blood pressure within the prehypertensive range. Among the included trials, there was little heterogeneity for risk reduction in incident strokes.

[Article 9]

**Feasibility of treating prehypertension with an angiotensin-receptor blocker.**

**BACKGROUND**

Prehypertension is considered a precursor of stage 1 hypertension and a predictor of excessive cardiovascular risk. We investigated whether pharmacologic treatment of prehypertension prevents or postpones stage 1 hypertension.

**METHODS**

Participants with repeated measurements of systolic pressure of 130 to 139 mm Hg and diastolic pressure of 89 mm Hg or lower, or systolic pressure of 139 mm Hg or lower and diastolic pressure of 85 to 89 mm Hg, were randomly assigned to receive two years of candesartan (Atacand, AstraZeneca) or placebo, followed by two years of placebo for all. When a participant reached the study end point of stage 1 hypertension, treatment with antihypertensive agents was initiated. Both the candesartan group and the placebo group were instructed to make changes in lifestyle to reduce blood pressure throughout the trial.

**RESULTS**

A total of 409 participants were randomly assigned to candesartan, and 400 to placebo. Data on 772 participants (391 in the candesartan group and 381 in the placebo group; mean age, 48.5 years; 59.6 percent men) were available for analysis. During the first two years, hypertension developed in 154 participants in the placebo group and 53 of those in the candesartan group (relative risk reduction, 66.3 percent; P<0.001). After four years, hypertension had developed in 240 participants in the placebo group and 208 of those in the candesartan group (relative risk reduction, 15.6 percent; P<0.007). Serious adverse events occurred in 3.5 percent of the participants assigned to candesartan and 5.9 percent of those receiving placebo.

**CONCLUSIONS**

Over a period of four years, stage 1 hypertension developed in nearly two thirds of patients with untreated prehypertension (the placebo group). Treatment of prehypertension with candesartan appeared to be well tolerated and reduced the risk of incident hypertension during the study period. Thus, treatment of prehypertension appears to be feasible. (ClinicalTrials.gov number, [NCT00227318](http://clinicaltrials.gov/show/NCT00227318).).

[Article 10]

**The Prevalence of Prehypertension and Hypertension Among US Adults According to the New Joint National Committee Guidelines**

***New Challenges of the Old Problem***

**Background**: The recently released Seventh Report of the Joint National Committee (JNC) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure provides a new classification of blood pressure levels. Little is known about the current situation of elevated blood pressure in the United States, according to the new guidelines.

(…)

**Results**: Elevated blood pressure is a serious problem in the United States. Approximately 60% of American adults have prehypertension or hypertension, and some population groups, such as African Americans, older people, low-socioeconomic-status groups, and overweight groups, are disproportionately affected. The prevalence of hypertension has increased by approximately 10 percentage points during the past decade. The awareness and appropriate management of hypertension among hypertensive patients remain low: 31% were not aware of their disease, only two thirds (66%) were told by health professionals to adopt lifestyle modifications or take drugs to control hypertension, and only 31% controlled their hypertension.

**Conclusions**: With 60% of the population affected, the United States is facing a serious challenge in the prevention and management of prehypertension and hypertension. People’s awareness and control of hypertension remain poor. This study highlights the seriousness of the problem and the importance of promoting lifestyle modifications.

(…)

In conclusion, this study shows that the United States is facing a serious challenge in the prevention and management of prehypertension and hypertension, since according to the new JNC guidelines 60% of the US population is affected by the condition. However, awareness and control of hypertension in the United States remain poor. Our findings highlight the seriousness of the problem and the importance of promoting appropriate lifestyle modifications. The new guidelines should serve as a wake-up call to reinvigorate the efforts of the general public, clinicians, and public health care professionals to prevent and control HBP in the United States.