

Is 2015 the Primetime Year for Prehypertension? Prehypertension: A Cardiovascular Risk Factor or Simply a Risk Marker?

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How Important is Hypertension for World Health?

The Comparative Risk Assessment module of the World Health Organization's Global Burden of Disease 2000 study¹ conducted a systematic assessment of changes in population health resulting from modifying exposure to 26 risk factors. These included atherosclerotic risk factors such as high blood pressure, smoking history, high cholesterol, high body mass index and physical inactivity, which were examined in over 55 million inhabitants of dozens of developing and developed regions of the world.¹ The message was clear: Hypertension is the single most important contributor to the global burden of mortality and morbidity in both developed and developing countries and the most important cardiovascular (CV) risk factor.

Why is Hypertension the Leading Risk Factor for World Health?

The relationship of systolic blood pressure (BP) to CV mortality was evaluated in the Prospective Studies Collaboration, the largest meta-analysis of its kind encompassing 1 million participants 40 to 89 years of age. Systolic BP was shown to be a powerful risk factor for stroke and ischemic heart disease mortality with doubling of fatal CV disease for every 20 mm Hg increment in SBP across fourth through 8 decades of life.² Most importantly, the aforementioned meta-analysis informed us that systolic BP is strongly and directly

related to vascular and overall mortality, without a threshold effect down to a BP of 115/75 mm Hg.²

Is it Time for Change?

A 50-year-old man with a BP of 135/80 mm Hg is twice as likely to die from a stroke as his counterpart with a BP of 115/80 mmHg. However, both subjects are considered non-hypertensive since the arbitrary cutoff for hypertension of 140/90 mm Hg is not reached. So, how can we better differentiate between these 2 subjects with different CV prognoses?

Over 12 years ago, the Seventh Report of the Joint National Committee on Prevention, Diagnosis, Evaluation and Treatment of High BP (JNC 7)³ defined a new BP category, prehypertension, a BP between 120/80 and 139/89 mm Hg that specifically identifies a higher-risk subject with BP higher than optimal BP but yet lower than the arbitrary cutoff for hypertension.

Why Should we Recognize Prehypertensive Subjects With a Separate BP Category Compared to Normotensive Subjects?

First, they are likely to become hypertensive over time, especially if they are of African-American descent.^{4,5} Second, they have a higher CV risk compared with normotensive subjects with a BP <120/80 mm Hg.² Third, the JNC 7 recommended a comprehensive therapeutic lifestyle modification strategy in prehypertensive subjects designed to reduce the risk of developing hypertension⁶ based on a plethora of studies. On the other hand, the JNC 8 did not address this prehypertensive group⁴ primarily because the management of prehypertension was not one of the key questions addressed by the JNC 8 committee.

Recent Meta-Analysis by Huang et al: What is New and What is Unique?

A recent meta-analysis in the *Journal of the American Heart Association*⁷ provided an interesting new perspective on the

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importance of prehypertension as a CV risk marker in different parts of the world. Huang et al aimed to characterize the association between prehypertension and coronary heart disease (CHD) risk examining the totality of evidence from multiple studies conducted worldwide and to compare the strength and magnitude of this association between Asians and Westerners (United States and Europe). A search of PubMed and EMBASE databases by Huang et al identified 17 prospective cohort studies inclusive of 591,664 participants, which assessed the relationship between prehypertension and CHD risk. Of those, 10 studies were conducted in Asian countries—Turkey, Japan, China, Iran, and India—and 7 in Western countries—the United States, France, Germany, and Serbia. The 2 key findings of this meta-analysis were: (1) prehypertension, even in the low range 120 to 129/80 to 84 mm Hg is associated with a significantly increased CHD risk and (2) the increased CHD risk is greater among Westerners than Asians (70% versus 25% greater CHD risk, respectively). Notably, prehypertension was associated with a higher population attributable risk in Westerners compared to Asians (24% versus 8%, respectively), suggesting that the potential impact of elimination of prehypertension—from a CHD standpoint—is significantly greater in Westerners.⁷

The present study by Huang et al⁷ has important methodological strengths over previous meta-analyses:

First, the quality of each of the included studies was rated using a robust and standardized methodology. All 17 included studies were deemed to have good or fair quality.

Second, only prospective cohort studies with multivariate adjusted CHD relative risk estimates were included to tease out the net independent effect of pre hypertension regardless of other risk factors.

Third, extensive sensitivity analyses were conducted and demonstrated the consistency of the findings across multiple study and patient's characteristics, adding to the overall validity of the results of this meta-analysis.

In-Depth Review of Huang's Meta-Analysis

Huang's meta-analysis⁷ provides an opportunity to re-examine the CHD relative risks among Westerners and Asians as summarized by Huang et al.⁷

Of the individual studies conducted in the United States and Europe, it is interesting to note that:

1. There is consistency in the directionality of the association between prehypertension and CHD with all studies showing an increased CHD risk.
2. There is consistency in the statistical significance of the association of prehypertension with CHD. All but 2 studies with the smallest sample sizes showed a statistically significant increase in CHD risk in prehypertension among

Westerners. On the other hand, 8 of 10 studies in the Asian countries failed to show a statistically significant association between prehypertension and CHD risk, including those with very large sample sizes.

Thus, there are clear reasons and good evidence to conclude that the association of prehypertension with CHD risk is more consistently and conclusively demonstrated in Western countries. However, this association is inconsistent, weak in magnitude, and unproven in many individual studies in Asians. These observations in our judgment cast considerable doubt on a genuine association between prehypertension and CHD in Asian countries.

Limitations and Challenges of Huang's Meta-Analysis

As we examine the individual studies included in Huang et al's meta-analysis, it becomes apparent that the distinction between Asians and Westerners is limited by significant heterogeneity within each of these groups. The 4 included US studies, Framingham Heart Study,⁸ Atherosclerosis Risk in Communities (ARIC) Study,⁹ Women's Health Initiative,¹⁰ and Strong Heart Study¹¹ have widely different populations. Similarly, the Asian studies⁷ were conducted in widely different countries across the Asian continent, from Turkey and Iran in the Middle East to India, Japan, and China in the South and Far East corners of Asia with very different baseline CV disease risks.

An important limitation of this meta-analysis⁷ is the focus on the CHD component of the overall CV risk and not considering ischemic stroke, for example, which is an important hard CV outcome. Huang et al recently reported that after adjusting for multiple CV risk factors, prehypertension remains associated with stroke morbidity.¹² Given higher stroke risks among Asians, the public health impact of prehypertension may not be lower among Asians when overall CV risk including stroke is considered.

Although some of the individual US studies included in the meta-analysis attempted to evaluate the impact of ethnicity and/or race, most of these evaluations were either lacking or significantly limited by the small sample size of the subgroups of Asian-Americans included. For example, the ARIC study⁹ combined Asians and Hispanics with Caucasians and simply reported on blacks versus non-blacks highlighting the higher CVD risk in the latter group. The Women's Health Initiative¹⁰ was the only US study in which the association of prehypertension and hypertension with CHD was evaluated in different ethnic groups and its findings are therefore interesting to examine in the context of the main findings by Huang and colleagues' meta-analysis. Asian-Americans had consistently higher CV disease hazard ratios—>8-fold in hypertensive and

>3-fold in prehypertensive subjects—compared with just 2.4 and 1.5-fold, respectively, in white Americans.¹⁰ However, the small sample size of the Asian and Pacific Islanders in this study (2.4% of the entire population) contributed to the failure of these large differences in CV risks to translate into clinically significant differences in outcome. These findings are, however, both surprising and difficult to reconcile with the conclusions of the meta-analysis by Huang et al⁷

Is Prehypertension an Independent Causative Risk Factor for CHD or Simply a Risk Marker?

Cohort studies are observational studies and are important in evaluating associations between risk markers or risk factors—the exposure of interest—and incidence of the disease of interest. However, to demonstrate causality, a variety of criteria should be satisfied.¹³

We critically review below the classical and widely acceptable Bradford Hill's causality criteria as they apply to the association between prehypertension and CHD outcomes:

1. Strength of association: "A strong association is more likely to have a causal component than is a modest association." For Western studies, the magnitude of the association ranges from 17% to a >100% excess risk across individual studies and amount to an overall 70% excess CHD risk, supporting a strong association. However, the modest 25% excess CHD risk among Asians with prehypertension is not consistent with a strong association, especially when we factor in unknown confounders and possible residual confounding effect after multivariate risk adjustment.
2. Consistency: "A relationship is observed repeatedly." Here lies the major drawback for Asian studies: many individual Asian studies did not report statistically significant associations between prehypertension and CHD risk.
3. Specificity: "A factor influences specifically a particular outcome or population." Specificity of the association of prehypertension and CHD is supported by multivariate risk-adjusted analyses which tease out known confounders of the association of prehypertension and CHD but unknown confounders cannot be adjusted for in observational studies.
4. Temporality: "The factor must precede the outcome it is assumed to affect." Temporality is supported by cohort studies in which subjects had no CV disease at study entry: only 4 of the included studies excluded such patients but study conclusions were similar with or without baseline CV disease.
5. Biological gradient: "The outcome increases monotonically with increasing dose of the exposure or according to a function predicted by a substantive theory." Greater relative risks (RR) of CHD with high-range prehypertension compared with low-range hypertension supports a biological gradient. However, the difference in RR between low- and high-range prehypertension is small—1.27 (95% CI of 1.07 to 1.50) versus 1.58 (95% CI of 1.24 to 2.02)—and non-significant.
6. Plausibility: "The observed association can be plausibly explained by substantive matter (eg, biological) explanations." The relation between prehypertension and CHD has not been well explained. Studies on atheroma progression are small, few and inconsistent in confirming the plausibility of this association.^{14,15}
7. Coherence: "A causal conclusion should not fundamentally contradict present substantive knowledge." The association between prehypertension and CHD is supported by the previously reported consistent and strong relation between BP and CHD risk down to a BP of 115/75 mm Hg.²
8. Experiment: "Causation is more likely if evidence is based on randomized experiments." This criterion is not fulfilled: the few randomized controlled clinical trials in prehypertension have reported inconsistent effects on atheroma progression^{14,15} and no randomized clinical trials have evaluated hard clinical outcome endpoints in prehypertension.
9. Analogy: "For analogous exposures and outcomes an effect has already been shown." Susser¹⁶ interpreted this criterion as follows: "when one class of causal agents is known to have produced an effect, the standards for evidence that another agent of that class produces a similar effect can be reduced." The wealth of the evidence supporting the association of hypertension with CHD² favors an association between a similar (or analogous) exposure—prehypertension—and CHD.

We therefore conclude—based on the totality of evidence—that the association between prehypertension and CHD is stronger and more compelling among Westerners than among Asians and is not—in our judgment—a causal association, especially among Asians. Thus, prehypertension is a CHD risk marker especially among Westerners but not a CHD risk factor.

So, What are the Clinical Implications of This Recent Meta-Analysis?

Should a prehypertensive subject be monitored more closely? The answer is yes. It is reasonable to monitor BP more closely in prehypertensive subjects since a significant proportion of them will later develop hypertension^{3,17,18}

Should a prehypertensive subject start any specific treatment? The answer is yes: lifestyle changes generally recommended in the overall population³ should be further emphasized in these subjects,³ in our opinion. The JNC 7 guideline recommendation for lifestyle changes in prehypertension is supported by the recent meta-analysis since prehypertension is a marker for an increased CHD risk, especially among Westerners. However, no pharmacological treatment is currently recommended by any medical society in the general population with prehypertension,^{3,6,17,18} a recommendation that is supported by our conclusion that prehypertension—albeit a CHD risk marker—has not been proven to be a causal CHD risk factor requiring specific treatment per se. Tempting as it might be to initiate pharmacologic therapy in prehypertensive subjects, the published clinical trials have cast doubt to any long-term benefit from a short-term pharmacologic intervention.^{14,15} Overall, the risk-benefit ratio and the value of such treatment in this subpopulation remain controversial.

Should we wait for BP to exceed the arbitrary cutoff of 140/90 mm Hg to start pharmacologic treatment to reduce CV risk? The answer is yes. The JNC 8 panel⁶ recommends starting antihypertensive drug therapy if BP is $\geq 140/90$ mm Hg in patients ≤ 60 years and if BP is $\geq 150/90$ mm Hg in patients >60 years.⁶

So, is 2015 the primetime year for prehypertension? The answer is yes. We are READY and SET but we do not have the evidence to GO with no proven therapy in sight for prehypertension. We should await considerably more research, particularly randomized controlled interventional clinical trials in prehypertensive subjects before recommending anything beyond BP monitoring and therapeutic lifestyle change as was initially recommended in JNC 7 over 12 years ago.

Disclosures

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