INTRODUCTION

A study done in 1939 observed that there was a sharp increase in mortality in individuals with BP measurements greater than 140/90 mmHg, giving rise to the usual clinical definition of hypertension. The investigators also observed that systolic BP in the range 120-140 mmHg, especially in younger individuals, was associated with progression to definitive hypertension and cardiovascular disease later in life, systolic BP in this range was first referred to as having ‘prehypertension’.

This concept of prehypertension, defined as systolic BP of 120-139 mmHg and/or a diastolic BP of 80-89 mmHg was once again incorporated into guidelines for the management of BP by the Seventh Report of the Joint National Committee (JNC 7). The objectives of creating such a category in the classification was to increase awareness of the importance of identifying individuals in whom early intervention by adoption of healthy lifestyles could lower BP and thus decrease the rate of progression to hypertensive levels, in order to reduce risk of cardiovascular disease. An additional rationale for use of this terminology was the greater likelihood of the affected individual to follow healthcare recommendations.

The evidence for creating this terminology came from the results of two landmark trials. A meta-analysis, that included approximately 1 million individuals from 61 long-term epidemiological studies and the longitudinal data from the Framingham Heart Study (FHS), which demonstrated that mortality from ischemic heart disease and stroke in individuals aged 40-89 years increases in a log-linear relationship with increases in both systolic and diastolic BP, for each 20 mmHg increase in systolic blood pressure or 10 mmHg increase in diastolic blood pressure over 115/75 mmHg, there is a twofold increase in mortality associated with coronary artery disease and stroke.

Arguments against using the use of this term was the fact that there is in homogeneity within this category because the risk of progressing to hypertension and developing cardiovascular events is higher in patients with BP 130-139/85-89 mmHg range than in those with BP 120-129/80-84 mmHg; also there were concerns that the term prehypertension would create anxiety among the general public.

EPIDEMIOLOGY

Prehypertension is a very commonly prevalent in the general population. The Third National Health and Nutrition Examination Survey (NHANES III) reported that the overall prevalence of prehypertension in the US was 31%, higher in men than in women, and was higher in obese than in normal weight persons. Similar data have been reported from India. A recent study from an affluent urban population in north India found a prevalence of prehypertension as 31%. Among urban residents >18 years living in Chennai the prevalence of prehypertension was reported as 47%. In the first study the prevalence of hypertension increased significantly from age group 30-39 to 60-69 years. In contrast, prehypertension was highest in the age group of 30-39 years (36%).
CARDIOVASCULAR RISK AND PREHYPERTENSION

Risk Factors
Prehypertension is associated with the same traditional cardiovascular risk factors as hypertension, such as obesity, diabetes mellitus and dyslipidemia. Studies from all over the world have shown that, increasing age, body mass index, waist hip ratio and impaired glucose tolerance/diabetes are independent risk factors for development of both hypertension and pre hypertension.6,7,8 Number of population based studies have found significantly higher levels of nontraditional cardiovascular risk factors like C-reactive protein, tumor necrosis factor, amyloid-α, homocysteine and white blood cell counts in prehypertensive individuals as compared to normotensive subjects.9,10 These studies clearly demonstrate that prehypertension is often associated with multiple cardiovascular risk factors, and because of risk factor clustering such individuals are predisposed for increased risk of cardiovascular disease in future.

Subclinical Disease and Cardiovascular Markers
Prehypertension is associated with subclinical cardiovascular disease, including both micro vascular and macro vascular pathology. Generalized retinal arteriolar narrowing an important sign of systemic hypertension, and a lower arteriolar: venular diameter ratio are more prevalent in prehypertensive individuals.11 Microalbuminuria a, direct result of increased glomerular capillary permeability and an manifestation of increased vascular permeability to proteins from other organs is associated with increased risk of cardiovascular disease and is more common in individuals with prehypertension.12 Prehypertensive individuals also often have increased evidence of subclinical atherosclerosis, manifested by increased common carotid artery intima-media thickness and increased calcium deposition in the coronary arteries.13,14 Prehypertension has also been associated with accelerated development of left ventricular (LV) hypertrophy and diastolic dysfunction. Population-based studies have reported significantly greater age-related increase in LV wall thickness, LV mass and LV hypertrophy, greater grades of diastolic dysfunction and increased left atrial sizes in prehypertensive individuals compared with individuals with normal blood pressure.15

Cardiovascular Morbidity and Mortality
In the WHI and Framingham Heart Study4,8, prehypertension, were associated with an increased incidence of cardiovascular disease, including myocardial infarction and coronary artery disease, stroke, hospitalization for heart failure and cardiovascular death. In MONICA study15 it was observed that the increment in cardiovascular risk associated with progression from normotension to prehypertension is similar to that associated with the progression from prehypertension to hypertension. Thus prehypertensive individuals are associated with increased risk of cardiovascular disease related morbidity and mortality on a long term basis.

TREATMENT

Nonpharmacological Treatments
Lifestyle modifications, such as weight loss, dietary alterations and exercise, have been shown consistently in randomized, controlled trials to effectively lower blood pressure and are recommended for patients with prehypertension.16-19 The DASH trial17 showed that BP was significantly reduced in prehypertensive and stage I hypertensive individuals by simply using a diet rich in vegetables, fruits, reduced saturated and total fat independent of dietary sodium restriction and weight loss. A sub study of the same trial18 showed that by reducing sodium intake (<100mmol daily) in addition to the previous dietary changes provided greater benefit than either approaches alone. Studies have also observed that multicomponent behavioral interventions incorporation and increasing physical activities have further reduced long term chances of developing artery disease. Thus early adoption of these approaches would not only lower BP but also prevent progression to hypertension with reduction in target organ damage and cardiovascular events. However, the incorporation of healthier lifestyle into everyday life has been difficult to maintain in the long. The largest population-based experience of lifestyle modification as a strategy to reduce cardiovascular risk factors, cardiovascular disease and mortality is from Finland ,where by using a comprehensive community-level approach that encompassed the health and other services like voluntary organizations, local media, businesses (including the food industry) and changes to public policy, demonstrated a reduction in mortality from coronary artery disease by 55% in men and by 68% in women over a 20 year period(1972-1992)19.

Pharmacological Treatments
Treatment of prehypertensive patients with antihypertensive agents in addition to nonpharmacological measures has been explored in two prospective, randomized clinical trials. The TROPHY study tested whether treatment with the angiotensin II receptor antagonist candesartan can prevent or delay the transition from prehypertension to stage 1 hypertension.20 Prehypertensive individuals were
randomly assigned to receive candesartan or placebo for 2 years, followed by 2 years of placebo for all participants. During the first 2 years, the risk of developing hypertension was reduced by 66.3% in the participants who received candesartan compared with the placebo group; the magnitude of risk reduction decreased to 16% by year 4, but was still statistically different from placebo. The treatment was well tolerated. TROPHY provided the first demonstration that pharmacological treatment for patients with prehypertension is safe and at least partially effective in reducing the risk of hypertension. However, no difference in the occurrence of cardiovascular events was observed between the two treatment groups and also the trial was not sufficiently powered to detect such a difference, had it occurred. In the PHARAO trial the effect of ramipril on preventing or delaying hypertension in individuals with prehypertension was studied. Participants with prehypertension were randomly assigned to receive ramipril or placebo and were followed for 3 years.

Hypertension developed in 31% of participants in the ramipril group and 43% of those in the placebo group, with a statistically significant 34% reduction in risk for the ramipril group although the incidence of cerebrovascular and cardiovascular events was low and not significantly different between groups.

Blood pressure control is an important target in patients with established atherosclerotic disease, and treating blood pressure to a prehypertensive level has a less favorable effect on disease progression than treatment to normotensive levels. In a sub study of the CAMELOT trial, patients underwent coronary intravascular ultrasound examination at baseline and after 2 years of amlodipine, enalapril, or placebo therapy. Patients who received active treatment and who achieved BP values within the prehypertensive range had no major change in atheroma volume, whereas those who became or remained hypertensive had significant increase in atheroma volume while who achieved normal blood pressure values had a significant decrease in atheroma volume. This result was the first demonstration that lowering of systolic BP to ≤120 mmHg-a level below the prehypertensive range-effectively reduces intermediate end points of cardiovascular disease. This finding enabled the American Heart Association-American College of Cardiology to recommend a blood pressure goal of <120/80 mmHg for patients with coronary artery disease but in recent trials (ACCORD-BPLA, INVEST) cardiovascular end points have been clearly shown to worsen if BP is brought to less than 120/80mmHg as compared to prehypertensive levels in patients with diabetes mellitus and coronary artery disease. Therefore pharmacological treatment of prehypertensive individuals remains a matter of debate. Arguments against the use of antihypertensive drugs for prehypertension include the lack of evidence that they reduce target organ damage and cardiovascular morbidity and mortality in these patients; that they are safe and cost effective when administered over many decades, as would be required to treat young individuals with prehypertension. Additional questions concern appropriate choices and doses of agents and duration of treatment. Arguments in favor of the use of antihypertensive drugs for prehypertension are that the drugs are more convenient and more likely to be adhered to than complex lifestyle-modifying regimens and that the drugs are already accepted for use in certain high-risk individuals with prehypertension i.e. in those with BP ≥130/80 mmHg and with diabetes mellitus, chronic kidney disease or coronary artery disease but not being too aggressive so as to lower BP < 120/80mmHg. In the absence of further information about these issues and in light of the fact that lifestyle approaches favorably influence global cardiovascular risk as well as BP, this currently remains the first choice for the treatment of individuals with prehypertension who do not have comorbid conditions that would mandate BP reduction by use of pharmacological agents. Patients at high risk of cardiovascular events, such as those with diabetes mellitus, chronic kidney disease or coronary artery disease, clearly benefit from aggressive intervention, and pharmacological treatment should be administered to these patients if BP exceeds 130/80 mmHg with a caution of not reducing BP levels < 120mmHg.

CONCLUSIONS

Individuals with prehypertension have an increased risk of full-blown hypertension, target organ damage and cardiovascular-related morbidity and mortality. Lifestyle modifications that lower BP reduce morbidity and mortality associated with cardiovascular events, and is recommended for all patients with prehypertension. Pharmacological treatment reduces progression from prehypertension to hypertension, but more studies are needed to determine the effects of pharmacological treatment on target organ damage and cardiovascular-related morbidity and mortality. Further studies are also needed to determine the safety and cost-effectiveness of medical interventions, and to determine whether particular drug classes are more effective than others in this patient group.
REFERENCES


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