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Review Article

PREHYPERTENSION: WHAT IS THE CURRENT STATUS?

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ABSTRACT
Cardiovascular disease (CVD) risk is a continuum across blood pressure. The term prehypertension was introduced because it is now recognized that blood pressure readings between what is deemed optimal and hypertension is associated with increased CVD risk. The prevalence of prehypertension is high and the progression to hypertension is also high. Prehypertension is also commonly associated with other CVD risk factors namely dyslipidaemia, dysgylcaemia and overweight/obesity. Eighty-five percent of prehypertensives have one other or more CVD risk factor compared to normotensives. A recent study has shown a reduction in the development of hypertension from prehypertension with the use of an angiotensin receptor blocker. Unfortunately to date, the impact of treatment of prehypertension on CVD outcome is still unknown except in those with high CVD risk like diabetes or established CVD. However this does not mean nothing can be done for those with prehypertension. The aim of managing prehypertension is to lower the BP, prevent progression to hypertension and to prevent BP related CVD deaths. Lifestyle changes can reduce BP and this by itself can lower CVD risk. Until more evidence about other modalities of treatment become available this is a sensible and cost-effective way to manage prehypertension.
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BACKGROUND

The term "prehypertension" was first introduced when the JNC 7[1,2] was launched at the American Society of Hypertension annual scientific conference in 2003. It caused tremendous discussions, amongst which were many objections to this new terminology. It was argued that this new definition of "illness" would impact an individual's employability, his life as well as medical insurance coverage and perhaps even converting what was an otherwise well person into a sick one.

Nevertheless, this term was introduced as part of the categorization of hypertension because it was recognized that there is still an excess cardiovascular disease (CVD) risk at levels of blood pressure (BP) deemed previously to be "normal" or "high-normal". The rationale for this new term was to bring to the attention of doctors and public health the need for more strenuous efforts at prevention of hypertension.

DEFINITION AND EPIDEMIOLOGY

Prehypertension is defined as systolic BP (SBP) of ≥120-139 mmHg and/or diastolic BP (DBP) ≥ 80-89 mmHg.[1,2] This is a change from the definition in JNC-6[3] for the reasons outlined above. The Malaysian Clinical Practice Guidelines Management of Hypertension 2008[4] has also adopted this definition. However the 2007 European Society of Hypertension (ESH) and European Society of Cardiology (ESC)[5] maintains the previous definitions of optimal, normal and high normal (Table 1).

Table 1. Definition and classification of hypertension

	JNC-6 and 2007 ESH and ESC definition			JNC-7 and Malaysian CPG definition		Prevalence in Malaysia,%
Category	Systolic		Diastolic	Definition		
Optimal	<120	and	<80	Normal		32%
Normal	<130	and	<85	Pre-hypertension	120-139/80-89	37%
High Normal	130-139	and/or	85-89			
Hypertension				Hypertension		
Stage 1	140-159	and/or	90-99	Stage 1		20%
Stage 2	160-179	and/or	100-109	Stage 2	≥160/100	12%
Stage 3	>180	and/or	>110			

Whichever definition one adopts there are a few common epidemiological observations namely;

- The prevalence of prehypertension is high. In the US, it is estimated to be around 31%[6] and in Malaysia it is around 37%.[7,8] This prevalence is even higher than the prevalence of hypertension itself.[6,7]
- Women are less likely to have prehypertension (23% in women versus 40% in men) This is a surprising finding.[6,9]
- Prehypertension is associated with overweight/obesity.[6,9] With the epidemic of obesity, the prevalence of prehypertension will rise and also reach epidemic proportions.
- Those age 60 and above are less likely to have prehypertension than younger individuals (24% in older versus 34% in younger individuals).[6] However this is not because raised BP is not as common in older individuals but because the majority (65%) of older individuals would already have hypertension.
- Prehypertension is commonly associated with other CVD risk factors namely dyslipidemia, dysgylcemia and overweight/obesity. Eighty-five percent of prehypertensives have one other or more CVD risk factor compared to normotensives.[9,10]
- Prehypertension progresses to hypertension at a high rate of 19% over 4 years.[11] One study showed an even higher progression of 40% over 2 years.[12]
  - The rate of progression also depends on the level of BP and age of the individual. Those with "high normal" (BP 130-139/85-89 mm Hg) progresses to hypertension at the rate of 43% over 4 years while those with lower BP (120-129/80-84 mmHg) does so at 20%.[11]
  - BP rises with age and the lifetime risk from age 65 of getting hypertension is nearly 100% over the next 20 years. Hence it is not surprising that those 65 years and older with prehypertension progresses at the rate of 42% versus a lower rate of 27% in the 35-64 age group.[11]
  - In other words, older individuals and those with higher BP levels are at greater risk to progress to hypertension.[11]
- Prehypertensives have an increased risk of CVD (relative risk RR 1.32; 95% confidence interval 1.05-1.65) compared to normotensives.[13]

EXCESS CVD RISK ASSOCIATED WITH PREHYPERTENSION

It is well known that the risk of CVD events rises with rises in BP and this risk is a continuum.[14] Consequently, those with prehypertension has twice the risk of someone with a SBP of 115 mmHg of getting coronary heart disease or stroke.[15] In fact there is a 27% increase in all cause mortality and a 66% increase in CVD mortality in prehypertensives compared to normotensive individuals. Thirty-two percent of BP related deaths occur in those with SBP of 110-139 mmHg.[10]

Although the absolute CVD events associated with prehypertension is relatively low, the morbidity, mortality and health care costs attributable to prehypertension is substantial because of the large number of prehypertensives involved. In a simulation of the NHANES I cohort with a follow-up of >20 years, it was estimated that 3.4% of hospitalizations, 6.5% of nursing home stays and 9.1% of deaths could be attributed to prehypertension.[16]

This excess CVD risk in prehypertension is due to subclinical atherosclerosis. Prehypertensives have

- increased coronary atherosclerosis[17]
- increased carotid and brachial intima-media thickness, a surrogate for atherosclerosis[18]
- elevated C-reactive proteins (CRP)[19,20]
- elevated tumour necrosis factor-α (TNF-α)[20]
- elevated serum homocysteine levels[20]
- elevated oxidized LDLcholesterol[18]
- microalbuminuria which is more common in prehypertension than normotension[21]
- presence of other inflammatory markers like interleukin[6,19,20]

Management of prehypertension

Obviously because of all the reasons above, the aim of management of prehypertension would be to

1. lower BP to within normal range
2. prevent a rise in BP with age
3. prevent BP related CVD events

Unfortunately to date, the impact of treatment of prehypertension on outcome is still unknown. However what is known is that in the treatment of hypertension, reduction of BP is associated with reductions in CVD events. There is abundant evidence that life-style changes[22] like dietary modification,[23] weight loss,[24-28] reduction in sodium intake,[24,27-29] regular physical activity[30-33] and limiting alcohol intake[34,35] can reduce BP (Table 2). While the BP lowering effect of each individual life-style change is modest, when taken together the benefit can be substantial. Furthermore it is also relatively free of much added costs and adverse events. Life-style changes not only benefit those with prehypertension but it will also benefit those with diabetes mellitus, dyslipidemia, the metabolic syndrome, overweight/obesity and other cardiovascular disease or risk.

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Table 2. Lifestyle modifications to prevent and manage hypertension[1]

Modification	Recommendation	~ SBP reduction
Weight reduction	Aim for BMI 18.5-25 kg/m^2	5-20 mmHg/10 kg wt loss
Sodium intake	< 100 mmol Na/ 6 g NaCl (1 ¼ tsp salt)	2-8 mmHg
Physical exercise	Aerobic activity e.g. brisk walking 30-60 mins, minimum 3x/ wk	4-9 mmHg
DASH Diet	Rich in fruit, vegetable and low-fat diary products	8-14 mmHg
Alcohol	2 units/day in men, 1 unit/day in women	2-4 mmHg

DASH, Dietary Approaches to Stop Hypertension; SBP, systolic blood pressure
Note: For overall cardiovascular risk reduction, stop smoking. The effects of implementing these lifestyle modifications are dose- and time-dependent, and could be greater for some individuals

IS THERE A ROLE FOR PHARMACOLOGICAL TREATMENT OF PREHYPERTENSION?

There is again abundant evidence for the use of pharmacological agents in those with diabetes mellitus and chronic kidney disease and prehypertensive range of BP especially if it is ≥ 130/80 mm Hg.[1,36,37] For those with other established CVD like stroke,[38] coronary heart disease (CHD), there is also evidence that pharmacological treatment is beneficial.[39]

Whether treating prehypertension with pharmacological agents can prevent hypertension has been looked at in one study.[12] The use of an angiotensin receptor blocker, candesartan did reduce the risk of developing hypertension compared to placebo but this reduction was very minimal once the drug was withdrawn.[12.] One can surmise that pharmacological agents can delay the progression of prehypertension to hypertension but it did not alter or prevent the progression into hypertension.

The greater difficulty is whether prehypertension should be treated as primary prevention of CVD events in circumstances other than those above. Because there are no outcome studies of pharmacological treatment of prehypertension, one approach would be to do a global cardiovascular risk assessment using for example the Framingham Heart Study multivariate risk algorithm. If the risk is medium (10-20% 10-year risk) or high (> 20% 10-year risk) then pharmacological treatment in addition to life-style changes should be considered.[4,5]

WHAT IS THE WAY FORWARD?

The number of individuals with prehypertension is overwhelming. Evidence for the use of pharmacological agents on outcome in prehypertension is still lacking. It is unlikely that such studies will be done because it would be very costly as large numbers of prehypertensive subjects will need to be studied in randomized controlled trials. As such, currently pharmacological treatment is not the answer nor is it feasible. Besides the lack of evidence, the cost of treatment, the biochemical changes and potential adverse events may outweigh the benefits of treatment of prehypertension.

However while evidence about pharmacological treatment of prehypertension is not available, it should not prevent doctors and the public health from embarking on preventing hypertension. As evidence is available showing that lifestyle modification is effective, practitioners should devote more effort on providing counselling to patients with prehypertension. It is acknowledged that for a host of various reasons, doctors are not very proficient at providing this support. Ways to improve this is to provide more training for the practitioners and other health care professionals and even to reimburse doctors for their time in providing this efficacious management.

Doctors cannot work alone. Public health groups, the school curriculum as well as food provided to children, the media, the food industry and even local authorities (to provide more space for physical activities for example) need to get together to develop a system-wide approach. Besides all these strategies, legislation and polices are likely required to achieve the goals of preventing hypertension and ultimately reducing CVD morbidity and mortality.

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100 years ago: The first Malayan clinical trial in *Lancet*?

Fletcher W. Rice and beri-beri: preliminary report on an experiment conducted in the Kuala Lumpur Insane Asylum. *Lancet*. 1907;1:1776-9.

"*The lunatics are housed in two exactly similar buildings on opposite sides of a quadrangle surrounded by a high wall. On Dec 5th all the lunatics at that time in the hospital were drawn up in the dining shed and numbered off from the left. The odd numbers were subsequently domiciled in the ward on the east side of the courtyard and no alteration was made in their diet, they were still supplied with the same uncured rice (Siamese) as in 1905. The even numbers were quartered in the ward on the west of the quadrangle and received the same rations as the occupants of the other ward, with the exception that they were supplied with cured (Indian) rice instead of the uncured Siamese variety.*"

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http://www.jameslindlibrary.org/trial_records/20th_Century/1900_1920/fletcher/fletcher_commentary.html

"William Fletcher's experiment on inmates of a lunatic asylum in Kuala Lumpur, Malaya, lives on in medical memory as the definitive proof that certain types of rice were 'either directly or indirectly, a cause of beri-beri'. It was a rigorous experiment, mimicking several features of a modern randomized trial."

100 years later, beri-beri has not completely disappeared, as shown in the following study that investigate a beri-beri outbreak in Perlis.

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