*TOPIC HIGHLIGHT*

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# Prehypertension: Underlying pathology and therapeutic options

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## 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%. Many hypotheses are proposed to explain the underlying pathophysiology of PHTN. The most notable of these implicate the renin-angiotensin system (RAS) and vascular endothelium. However, other processes that involve reactive oxygen species, the inflammatory cytokines, prostglandins and C-reactive protein as well as the autonomic and central nervous systems are also suggested. Drugs affecting RAS have been shown to produce beneficial effects in prehypertensives though such was not unequivocal. On the other hand, drugs such as β-adrenoceptor blocking agents were not shown to be useful. 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.

**Core tip:** There is a current debate over the ideal means of intervening in prehypertension. Since it is the cardiovascular risk that constitute the basis for intervention in both prehypertension and hypertension, the review discusses the following points, that: (1) categorizing blood pressure levels is based on mere 20 mmHg brackets; hence this doctrine may be re-visited to include other cardiovascular risk factors to categorize patients regardless of their blood pressure level; (2) investigating the therapeutic potential of intervening in all pathophysiological processes associated with prehypertension; and (3) ascertaining the therapeutic value of the "Polypill" in prehypertensives as means of primary prevention.

## SEARCH AND ARTICLE COLLECTION METHOD

Initially, PubMed and Scopus were searched using the

key words prehypertension, epidemiology, and treatment (as such or in the form of derived terms as appropriate) alone and in combination, were used to identify a set of primary articles. Other searches using pertinent key words were conducted as required; such was particularly utilized during search for pathophysiologically-related publications. For example, treatment + prehypertension led to renin-angiotensin system, which led to angiotensin converting enzyme system, angiotensin converting enzyme inhibitors, angiotensin receptor blockers and so on. To the resulted articles we added our own collection. Reviews were used as another source to include more articles. All searches were limited to English language.

The main aim of this review was to provide an overall understanding of the current status of the medical profession opinion on prehypertension and to map the so far recommended or suggested therapeutic strategies. It also reflected on other potential therapeutic options. The selection of cited references was made to serve that aim.

## CONCEPTUAL OVERVIEW

### Definitions

The concept of prehypertension (PHTN) was introduced in 1939 by Robinson and Brucer who were first to draw attention to the range of blood pressure (BP) between 120-139 mmHg (systolic) and 80-89 mmHg (diastolic) as being of value in determining clinically overt hypertension (HTN)[1]. Almost three decades later, the same BP range was given the name "borderline hypertension"[2], then the name changed to "high-normal blood pressure" in 1997[3]. The name "prehypertension" was given in 2003[4]. The nomenclature went further by some authors[5] who categorized BP levels between 130-139/85-89 mmHg (the upper half of PHTN range) as "Stage 2" PHTN. Also, the upper half of the HTN range was given the name of "high normal" blood pressure by the European Society of Hypertension/the European Society of Cardiology[6].

HTN is defined as a systolic/diastolic pressure level of $\geq 140/90$ mmHg)[7,8]. HTN is a major world health problem and is among the most prevalent chronic conditions with rates that reach up to 70% of adult population in some countries[9] and is on the increase[10]. HTN has been identified as the leading global risk factor for disease burden[11] and it is considered to be the most important modifiable risk factor for coronary heart disease, stroke, congestive heart failure and end-stage renal failure[12].

### Salient issues pertaining to blood pressure and cardiovascular risk

Prior to start the discussion on the main topic of this review i.e prehypertension, there are a number of issues that are of significant value to this topic and they address the relationship of changes in BP and their correlation with cardiovascular (CV) morbidity and mortality. These are; the J-blood pressure curve concept; the central versus peripheral blood pressure relation with CV events; and the complex interaction of different antihypertensive

drugs on blood pressure and cardiac hemodynamics. A brief account of each of these follows.

### The J-blood pressure curve concept and cardiovascular risk

The "J-curve" concept describes the shape of the relationship between BP and the risk of CV morbidity or mortality[13]. Some authors consider the J-curve to be more correlated with diastolic blood pressure (DBP) than systolic blood pressure (SBP)[14] since most of coronary blood flow occurs in diastole[15]. Three pathophysiologic mechanisms have been proposed to explain the existence of a J-curve are: (1) low DBP could be an additional risk factor to coexisting or underlying poor health or chronic illness leading to increasing morbidity and mortality; (2) low DBP could be caused by an increased pulse pressure reflecting advanced vascular disease and stiffened large arteries; and (3) over-aggressive antihypertensive treatment could lead to too-low DBP and thus hypo-perfusion of the coronaries resulting in coronary events[13].

The J-curve concept is in line with the thought that BP has a continuous relationship with CV events such as myocardial infarction, stroke, sudden death, heart failure and peripheral artery disease as well as of end-stage renal disease[16-20] even at values such as 110-115 mmHg for SBP and 70-75 mmHg for DBP[21,22].

### Central systolic versus peripheral systolic blood pressure and cardiovascular events

In adults, peripheral SBP (pSBP) exceeds central (aortic) SBP (cSBP) by about 10 mmHg or more[23]. This difference is greater in younger subjects, during exercise and is affected by drug therapy[23]. Because cSBP and cPP are more closely related to the load on the heart and pulsatile stress on the coronary arteries than pSBP, they are suggested to be better predictors of CV events[24,25]. Additionally, it may be highlighted that the heart, kidneys, and major arteries supplying the brain are exposed to aortic rather than peripheral pressure. Therefore, there is a rationale to believe that CV events may be more related to central rather than brachial pressure[26].

The increase in central pressure from diastolic to systolic values is determined by the compliance of the aorta as well as the ventricular stroke volume. A high central pulse pressure (PP) is considered to be a marker of increased artery stiffness and represents a well-established independent predictor of CV morbidity and mortality[27-29] in hypertensive individuals and even in those considered as having normal BP[30]. PP significantly predicts major adverse CV events including unstable angina pectoris, myocardial infarction, coronary revascularization, stroke, or death[31]. An independent correlation between aortic PP and coronary artery disease was established in men, along with age and hypercholesterolaemia[32,33]. The late decrease in DBP after the age of 60, associated with a continual rise in SBP, is consistent with increased large artery stiffness. Higher SBP, if left untreated, may accelerate large artery stiffness and thus perpetuate a vicious cycle[21].

Indeed, central pressure was found to be more (than peripheral pressure) correlated with indicators such as carotid intima-media thickness[24,34,35] and left ventricular mass[35-37]. Also, aortic pulse pressure was found to be significantly and independently correlated with angiographically determined coronary artery stenosis[38] and more related to CV events than brachial pressure[24,39-41] and responds differently to certain drugs[25,42]. For example, it was found that the β-blocker, atenolol, is inferior to other major anti-hypertensive drug classes in preventing CV events. β-blockers exert differential effects on brachial *vs* central pressure which may help to explain the adverse findings with atenolol in outcome studies and provides support for the hypothesis that drugs which lower central pressure the most will be more effective[43-48].

### Antihypertensive drugs and cardiovascular events

The interaction of antihypertensive drugs on BP and coronary hemodynamics (and hence CV events) is complex. For example, not all antihypertensive drugs have similar effects on pulse pressure. Blockers of the renin-angiotensin system, calcium antagonists and diuretics improve arterial compliance and thus lower SBP more than DBP and therefore diminish pulse pressure. In contrast β-blockers, because they decrease heart rate, increase stroke volume would have a less favorable effect on pulse pressure than the other drugs. Yet, decreased heart rate may allow for more prolonged diastolic perfusion of the coronary vascular bed and *vice versa*; whereas, short-acting calcium antagonists and other arteriolar vasodilators (such as hydralazine, minoxidil) are prone to cause myocardial ischemia in susceptible patients[49].

Antihypertensive drugs that reduce left ventricular hypertrophy (LVH) and hypertensive vascular disease are more effective over the long term in improving coronary flow reserve than drugs that have little or no effect. Thus, blockers of the renin-angiotensin system, calcium antagonists as well as the diuretics, have been shown to reduce LV hypertension[50] and hypertensive vascular disease[51-53] and improve arterial compliance[54] better than β-blockers.

## EPIDEMIOLOGY OF PHTN

Many studies in various countries were performed to determine the magnitude of the PHTN rate. These have revealed that PHTN prevalence is considerable and it varies widely from country to country. For example, prevalence rate averages at 21.9% in China[55], at 32.8% in the Netherlands[56], at 34% in Taiwan[57], at 37% in the United States[58], at 40% in Ghana[59], at 48.2% in Oman[60] and at 52% in Iran[61]. Men[57-59,61] and blacks[62] are more likely to be affected than women or whites; respectively.

## CARDIOVASCULAR RISK OF PHTN

PHTN is not only a caveat to develop overt HTN, but it is a major health risk on its own also. Prehypertensives were repeatedly reported to be subjected to approximate-

ly double the risk of CVD independent of progression to HTN[58,63] in addition to other cardiovascular complications[64-66].

## PATHOPHYSIOLOGIC CHANGES ASSOCIATED WITH RAISED BP

This part of the review is intended to discuss briefly the significant pathophysiologic changes associated with the progressive increase in BP to provide the scientific premise for currently recommended interventions or another that is recommended by this review.

## INVOLVEMENT OF THE RENIN-ANGIOTENSIN SYSTEM (RAS)

### Effects of RAS on cardiovascular system in general

Angiotensin Ⅱ, an active peptide of the RAS, causes increase in BP and enhances oxidation of the low-density lipoprotein *via* stimulation of its type 1 receptor (AT1)[67,68]. It appears that it acts in this respect by inhibiting NAD(P)H oxidase-mediated oxygen synthesis and enhances antioxidant superoxide dismutase activity in the cardiovascular system and decreases nitric oxide (NO) bioavailability. The latter effect may be responsible, at least in part, for the beneficial effects of drugs inhibit RAS activity such as angiotensin converting enzyme inhibitors (ACEIs) or angiotensin Ⅱ type 1 receptor blockers (ARBs) that may act, eventually, by enhancing NO availability[69-71]. However, RAS blockade provides additional protective effect on cardiovascular function that cannot be solely explained by mere reduction of BP which is the action mediated by increasing NO availability[72].

In this context, it may be added that angiotensin-converting enzyme 2 (ACE2) converts angiotensin I to angiotensin (Ang)-1-9, that can be converted by ACE to a shorter peptide, Ang-1-7, which has an intrinsic vasodilator activity[73,74]. ACE2 have been described to be a potent negative regulator of RAS, counterbalancing the multiple functions of ACE, thus, it plays a protective role in the CV system and other organs[75].

Also, chronic activation of the RAS was shown to underlie HTN, insulin resistance, cardiac and renal disease, and polycystic ovarian syndrome and it serves as a link between obesity and low-grade systematic inflammation[76-80]. In addition, it is suggested that RAS contributes to the atherosclerotic process through angiotensin Ⅱ, which acts as a proinflammatory mediator directly inducing atherosclerotic plaque development and heart remodeling and exacerbate endothelial dysfunction[81,82]. On the other hand, blockade of RAS can offer protection from RAS-related metabolic diseases including diabetes[83-88].

The statement by Demirci *et al*[72] is further enforced by the observation that the ACE gene may be a determinant of serum ACE levels, but it does not appear to confer susceptibility to essential hypertension[89], since there are many factors that influence the genetic make-up of

blood pressure[90]. In addition, other environmental factors[91] may be involved in determining BP. Therefore, the possibility of drugs interfering in the RAS to be additionally interfering with any of these other factors cannot be eliminated.

### Effect of RAS on development of hypertension

The first report on the potential of early intervention to prevent HTN was in 1990[92]. The authors showed that inhibiting RAS by captopril (an ACEI) for two weeks may intervene in the progression of HTN in young "prehypertensive" spontaneously hypertensive rats (SHRs). Later, other studies have shown that transient inhibition of the renin-angiotensin system from two weeks of age in SHRs, either with ACEIs or with ARBs, diminishes the increase in BP for up to 21 wk after cessation of treatment[93]. While others reported that permanent treatment of SHRs from conception onwards with ACEIs completely prevented hypertension[94,95].

The ARBs losartan was reported to have beneficial effect in humans[96] and rats[97,98] similar to that of captopril in SHRs, specifically, as shown by another study that transient use of losartan resulted in a long-lasting improvement of arterial contractility, an effect that was linked to endothelium-dependent vasodilatation[92,98].

Paradoxically, other authors showed that decreased BP is accompanied by severe disruption of the normal vascular architecture of intrarenal arteries[99]. These authors concluded that, apparently interference with RAS during a crucial stage of development in SHRs can initiate this disturbance and may cause intrarenal vascular smooth muscle hyperplasia, suggesting the involvement of another trophic factor that is inhibited by angiotensin II under physiologic conditions. Such led other workers[72] to suggest that the efficacy of antihypertensive treatment is also influenced by age and the hypertensive stage of the investigate animals.

## INVOLVEMENT OF VASCULAR ENDOTHELIUM

The association between RAS and endothelium-dependent pathways in PHTN was suggested by more than one observation. It was shown that dysfunctional NO synthesis in PHTN may be a source of oxygen free radicals or reactive oxygen species (ROS) which may be an additive factor to develop overt HTN[100]. Jameson *et al*[101] reported that, endothelium-dependent relaxation of prehypertensive SHRs mesenteric arteries was impaired. Later, interleukin-1β (which induces inducible NO Synthase) was shown to cause a lower production of NO and a reduced generation of cGMP in these animals[102]. This observation was followed by demonstrating that lower NO level correlated with increased SBP in the same species[103]. Such was related to impaired NO production alone[104] or combined with an enhanced ROS activity which may contribute to progression of PHTN to HTN[105]. All these effects in-

dicate that endothelial vasodilator capacity is impaired in PHTN[106].

## INVOLVEMENT OF REACTIVE OXYGEN SPECIES (ROS)

It is stated above that ROS may add to developing overt HTN. Therefore, it is not surprising that antioxidant deficiency has been long implicated in HTN pathogenesis[107-109]; whereas, antioxidant treatment to reduce oxidative stress was shown to prevent development of HTN in SHRs[110]. Many studies have demonstrated that enhanced production of plasma free radicals may impair the physiologic function of vascular endothelium[111-113]. An action that may lead to increase in BP. Recently, the rationale for antioxidant trials in PHTN was reviewed by Nambiar *et al*[114].

## INVOLVEMENT OF THE INFLAMMATORY PROCESS: PROSTGLANDINS AND C-REACTIVE PROTEIN

Inflammation was also implicated in the development of HTN and in endothelial dysfunction either as a primary or a secondary event[115]. Inflammation, indicated by C-reactive protein (C-RP) level, was used to predict HTN among PHTN subjects[116,117]. In addition, prostaglandin E2 (an inflammatory cytokine) was particularly shown to enhance norepinephrine-pressor response in PHTN; an effect that was abolished by indomethacin (a prostaglandin synthesis inhibitor)[118].

## INVOLVEMENT OF THE AUTONOMIC NERVOUS SYSTEM

Eyal *et al*[119] suggested that α-adrenoceptors of SHRs are in a basic state of excitation even prior to the onset of overt HTN, *i.e.*, in PHTN. Prior to this observation, Fujimoto *et al*[120] demonstrated that β-adrenoceptor-mediated relaxation of arteries, in the same species, was diminished before and during development of HTN. The diminished relaxation may be because of defective hyperpolarization induced by these receptors[121]. In the same rat species, both the M3 cholinoceptors- and P2y-mediated relaxation was not altered[122] ruling out involvement of any other component of the autonomic nervous system apart from the sympathetic. However, β-blockers, compared to ACEIs, did not improve resistance arteries function after two years of use in human[123,124].

The underlying mechanism for the sympathetic involvement was also indicated by the presence of subsensitive presynaptic α2-adrenceptors which may lead to exaggerated norepinephrine secretion[125], an effect that may have a causal relevance to development of HTN[126]. Similarly, the β2-adrencceptor-mediated facilitation of neurogenic pressor response was found to be enhanced in prehypertensive SHRs, which may contribute to devel-

opment of HTN[127].

# INVOLVEMENT OF CENTRAL MECHANISMS

An impaired baroreceptor control of vascular resistance was implicated in SHRs[128] and such was thought to be a primary defect[129]. In humans, baroreflex was not found to be altered, but plasma norepinephrine positively correlated to BP and associated with subsensitive α- and β-adrenoceptors[130].

Another explanation of the sympathtic overactive state in PHTN/HTN was postulated by Kotchen *et al*[131]. It is based on the observation that brain NO, as a neurotransmitter, reduces sympathetic output, and systemic angiotensin Ⅱ activates NO-producing neurons. SHRs show higher gene expression of nNOS, probably, as a compensatory mechanism for increased BP. That hypothesis was supported by the finding that hypothalamic angiotensin Ⅱ-sensitive neurons activity was greatly enhanced in PHTN[132], and that the central component of the baroreflex was also impaired[133].

# INVOLVEMENT OF OTHER MECHANISMS

Other than RAS pathways should be investigated since not all the beneficial effects attributed to anti-RAS drugs (in HTN and PHTN) can be solely understandable by its mere reduction in BP. For example, RAS is activated by common comorbidity including type 2 diabetes, hyperinsulinemia and excess weight as well as it can be activated by a diet rich in carbohydrates and fats. Two clinical trials[134,135] have shown that ACEIs decrease the risk of developing type 2 diabetes in patients with HYN and/or vascular disease.

# THERAPEUTIC OPTIONS OF PREHYPERTENSION

## *Rationale for therapeutic intervention in PHTN*

PHTN and HTN are associated with a number of factors such as increased age, male gender, increased C-RP level and waist circumference[117,136]. These factors are positively correlated with the development of HTN[117]. Yet and despite the clear relationship between HTN and PHTN, treating HTN is unequivocally accepted, but the debate over the use of the term PHTN itself as a clinical category[137] or what type of intervention to be used in this case has not yet been concluded. The main reasons raising the thought of therapeutically intervening in prehypertensive subjects can be summarized as follows: (1) elevated systolic BP is the most important risk factor for cardiovascular, cerebrovascular, and renal disease[4,16,138]; (2) there is a strong association of cardiovascular mortality risk with BP[16]; (3) it is expected that many individuals with PHTN will, with time, become overt hypertensive patients[139]; and (4) for normotensive population, it was calculated that SBP increases at an average rate of about

0.5 mmHg/year[137].

## *Current suggested intervention strategies in PHTN*

In principle, intervening in PHTN is a form of primary prevention, which can be enacted in more than one way. One is by the use of proven and safe drugs; another is by inducing individual behavioral changes. The latter is an attractive option because of its inherent "natural" appeal, perceived low cost, simplicity and safety though may not be sustainable.

Primary prevention strategies that are directed towards the individual necessitate screening all individuals in order to identify those who are over a certain "threshold". That process is followed by subjecting individuals at risk to an appropriately "tailored" intervention to each of them which incurs high cost. In addition, risk prediction in primary prevention remains imprecise and may not reflect long-term risk[140].

At the community level, primary prevention may be endorsed by passing health policies, encouraging beneficial cultural attitudes and/or imposing environmental changes. This approach is more likely to have a greater impact on individual's health[141-144].

At present, it is agreed in principle, that prehypertensive subjects should be treated. However, there is a polarizing controversy on the means of intervention. Two main strategies are recommended; one is based on "Therapeutic Lifestyle Changes (TLCs)"[4], and the second is based on using antihypertensive monodrug therapy[5].

# TLCS

Previous[3] and current guidelines[5] advocate specific lifestyle modifications for prehypertensives. The most recent recommendations (JNC7 report)[4] are as follows: (1) maintain body mass index between 18.5 and 24.9 kg/m²; this is expected to reduce SBP by 5 to 20 mmHg for each 10-kg reduction in weight; (2) consume a diet rich in fruits and vegetables, as well as low-fat dairy products; this is expected to reduce SBP by 8 to 14 mmHg; (3) restrict sodium to no more than 6 g of table salt per day; this is expected to reduce SBP by 2 to 8 mmHg; (4) walk briskly at least 30 min per day or engage in other regular aerobic physical activity; this is expected to reduce SBP by 4 to 9 mmHg; and (5) reduce alcohol consumption; this reduces SBP by 2 to 4 mmHg.

## *Evidence for therapeutic effectiveness of lifestyle modifications*

The JNC 7 lifestyle changes are focused on weight loss, dietary restriction and exercise, which were supported by abundant clinical evidence. For example, weight loss[145], and salt restriction[146] have been shown to improve PHTN. Maintaining a body mass index between 18.5 and 24.9 kg/m² is expected to reduce SBP by 5 to 20 mmHg for each 10-kg reduction in weight[16].

Weight loss has been shown to be the most effective lifestyle modification strategy for prevention of hypertension[147]. Reductions in BP occur even without attain-

ment of normal body mass index. In a meta-analysis of 25 randomized, controlled trials, weight loss of 1 kg was associated with approximately 1 mmHg reduction in SBP and DBP in individuals with HTN[148]. Addition of antihypertensive medication has been shown to have an effect on BP reduction that is additive to that achieved by weight loss alone[148,149]. However, it has been shown that the type of medication prescribed may decrease the ability of the patient to lose weight[147].

Dietary pattern changes, in general[150] or specifically prescribed such as the Dietary Approaches to stop hypertension (DASH) plan[151,152] which uses a diet rich in fruits, vegetables, legumes, nuts, and low-fat dietary products and low in saturated fats, induced a significant lowering of BP. Adhering to the DASH diet can reduce BP by 8-14 mmHg, an effect that was augmented even further when dietary sodium was restricted. The OmniHeart Collaborative Research Group study[153] in which the DASH diet was modified to provide more protein and unsaturated fat and less carbohydrate, impressive reductions of BP were also achieved. The TOHP trial[147], in a substudy of the DASH trial also showed that by reducing sodium intake to less than 100 mmol in your daily diet, in addition to dietary changes provided greater benefit than either approach alone[154].

Similarly, there is ample evidence that exercise, independent of weight loss, decreases BP[154-157]. A number of clinical trials demonstrated that increased physical activity can lower BP independent of any effect on body weight, although this finding is not universal[158-160]. However, two meta-analyses concluded clearly that physical activity independently lowers BP[161,162]. In one of these meta-analyses, 27 of 50 studies reported results in nonhypertensive subgroups, which presumably include a large proportion of participants with PHTN[162]. Exercise alone has been associated with a 30% reduction in cardiac risk, making it similar to statin and antihypertensive interventions[163-166]. Hence, a number of studies have been performed to examine the effects of aerobic and/or resistance exercise on BP in hypertensive, prehypertensive, and normotensive groups, and a recent review has examined the relevant findings[167].

Nevertheless, some trials have shown that TLCs to have a modest and unsustainable impact to reduce CVD events when tested in large, long-term trials[152,168]. This observation has been challenged by the PREMIER trial[169] which studied the combined effects of diet, physical activity, and weight reduction in three groups of prehypertensive and hypertensive subjects over an 18-mo period. Although all three groups demonstrated significant reductions in BP in both prehypertensive and hypertensive subjects, the amount of decrease in the group given relatively minimal counseling was both surprising and gratifying in view of the previous difficulties with obtaining long-term behavioural changes to improve the cardiovascular risk status. These findings encourage adding counseling as an important early augmenting intervention to lifestyle modifications that may sustain beneficial therapeutic effect. This view is further supported with

the findings of the largest population-based experience of lifestyle modification as a strategy to reduce cardiovascular risk factors, CVD, and mortality. The study used 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. It demonstrated a reduction in mortality from coronary artery disease by 55% in men and by 68% in women over a 20-year period[170]. Furthermore, in a recent randomized clinical trial[171] it was found that subjects with increased BP who participated in an automated online self-management program resulted in improved BP among prehypertensive or hypertensive subjects. These findings emphasize the need to involve patients for a more sustainable outcome. Similar results were obtained in overt hypertensive patients, who, in a prospective cohort study received repeated nonpharmacological recommendations to follow low-salt and low-calorie diets and to do physical activities[172]. This study concluded that adherence to follow low-salt and low-calorie diets is associated with clinically relevant long-term BP reduction and better hypertension control in clinical setting.

Although the evidence on reducing alcohol intake and reduction in BP is equivocal[173,174], a meta-analysis of trials in this respect with many of the analysed trials included prehypertensives[175] suggest that reducing alcohol intake can independently lower SBP.

## THERAPEUTIC INTERVENTION WITH A MONODRUG THERAPY

All concluded studies that have been attempting to treat PHTN used one drug that affects the RAS in the form of ACEIs, ARBs or renin inhibitors. The use of other monotherapies such as β-blockers, was not shown to be, compared to ACEIs, effective in improving resistance arteries function after two years of use in human[123,124]. The involvement of RAS in PHTN and HTN was discussed earlier. This part of the review summarizes the outcome of clinical trials using drugs that affect RAS in this respect.

### Clinical trials with drugs affecting RAS: ongoing clinical trials

Two clinical trials are ongoing: (1) the first trial is the PREVER-Prevention trial[176], a controlled randomized, double-blind trial designed to include individuals with PHTN given chlorthalidone 12.5 mg plus amiloride 2.5 mg or placebo. The study is to investigate if early use of drugs in individuals with PHTN may prevent cardiovascular events, target-organ damage and the incidence of overt HTN. In the 2nd International Conference on Prehypertension and Cardiometabolic Syndrome (January 31 - February 3, 2013; Barcelona, Spain) the trial co-principal investigator (Fuchs FD) announced that PREVER has finished enrollment of 1053 patients. According to the study design, patients who are still prehypertensive after three months of recommended lifestyle changes are randomized to a low-dose combination of chlorthalidone

plus amiloride or to placebo. Preliminary results from the study[177] indicate that 659 (77%) of subjects remained prehypertensive and were randomized according to the study protocol; another 7.5% had abnormal lab values, and 6.2% had progressed to developing HTN, while 9% had seen their BP drop to within normal values; and (2) The second trial is the Chinese High Normal Blood Pressure (CHINOM) trial. The study has finished enrollment of 10689 patients with BP in the range of 130-139/85-89 mmHg and at least one other cardiovascular disease risk factor (but no established diabetes, renal or hepatic dysfunction, or history of stroke or CVD). The trial randomized patients to one of three parallel treatment groups: telmisartan 40 mg, indapamide 1.5 mg, or, in the third group, placebo or a combination pill of hydrochlorothiazide 12.5 mg, triamterene 12.5 mg, dihydralazine 12.5 mg, and reserpine 0.1 mg. The primary end point of the study is combined CV events (nonfatal stroke, nonfatal MI, and CVD death), while secondary end point addresses new-onset hypertension and new-onset diabetes. In the above mentioned conference, it was announced that the CHINOM trial is still awaiting the first results which may be still several years away. However, baseline characteristics of study subjects are showing that 70% of subjects enrolled actually have more than one cardiovascular risk factor with metabolic syndrome being the most common. More than three-quarters of participants are overweight or obese, 42% have high triglycerides, and over one-third have a family history of hypertension[177].

### Clinical trials with drugs affecting RAS: concluded clinical trials

The first clinical trial was the TRial Of Preventing HYpertension (TROPHY)[178,179] which examined whether early treatment of PHTN justified pharmacologic intervention with the use of an ARB (candesartan 16 mg daily) in HTN. TROPHY hypothesis to examine whether ARBs may be useful to treat PHTN was based on the following: (1) PHTN is a strong independent predictor of cardiovascular events; (2) growth factors mediated by stimulation of the sympathetic nervous system[180] and excess activity of RAS[181] tend to promote vascular hypertrophy by direct as well as hemodynamic effects. Antihypertension treatment with ACIs or ARBs, but not with β-blockers, has been reported to cause regression of arteriolar hypertrophy[123,124]; and and (3) despite intensive community efforts to promote healthy lifestyle, the prevalence of PHTN[182] in the United States is increasing.

Over a period of four years of TROPHY study, it was found that stage 1 HTN developed in nearly two thirds of patients with untreated PHTN (the placebo group). Treatment of PHTN with candesartan appeared to be well tolerated and reduced the risk of incident HTN during the study period. The authors concluded that, treatment of PHTN appears to be feasible.

Although the observations in this study indicate that candesartan may ameliorate BP in prehypertensives, a comment by the authors stated that they do not advocate

treatment of the 25 million people (in the United States) with prehypertension. They added that additional studies will be needed to ascertain whether this or other strategies involving early pharmacologic treatment of PHTN would positively affect clinical outcomes.

Another trial is the PHARAO study[183] which demonstrated that ramipril (an ACEI) given to prehypertensives reduced the risk of HTN by 34.4% compared to those not taking antihypertensive drugs; however, no differences were found in cardiovascular or cerebrovascular events. The study concluded that prehypertensives are more likely to progress to overt HTN than those with optimal or normal BP when treated with ACEIs.

A third trial, on the other hand, concluded that pharmacological therapy is indicated for some patients with PHTN who have specific comorbidities, including diabetes mellitus, chronic kidney disease and coronary artery disease[184], while another trial[185] did not support the use of antihypertensive drugs in "normotensive" subjects and that, ARBs might offer less protection against myocardial infarction than ACEs.

Most recently, the AQUARIUS trial[186] examined the effect of aliskiren (a renin inhibitor) on progression of coronary atherosclerosis in a double-blind, randomized, multicenter trial study. It concluded that among participants with PHTN and coronary artery disease, the use of aliskiren compared with placebo did not result in improvement or slowing of progression of coronary atherosclerosis and that their findings do not support the use of aliskiren for regression or prevention of progression of coronary atherosclerosis.

## INTERVENTION WITH MULTIDRUG FORMULATIONS: SHOULD THE "POLYPILL" BE CONSIDERED IN PHTN?

### What is the "Polypill"?

The "Polypill" is a multidrug formulation with modified drug combinations containing drugs such aspirin, statins, β-blockers, ACEIs and ARBs; all of which are of proven value in reducing CVD morbidity and mortality. Approximately, half of the decline in cardiovascular mortality observed in developed countries during the last two decades is attributable to medical therapy using these types of drugs[187].

The introduction of the Polypill idea was not intended for use in PHTN, rather it was for reducing the burden of CVD in economically disadvantaged individuals to reduce cost and improve adherence. It was meant to be applied to entire or large segments of the population. The reasons behind innovating the Polypill (see below) were, in effect, the same as those for intervening with PHTN, the authors suggest considering to include prehypertensives in future Polypill clinical trials to ascertain the potential benefit of using the Polypill in these subjects.

### Rationale behind the polypill composition

Some of the main relevant reasons for introducing the

Polypill are summarized as follows: (1) cardiovascular disease is the major cause of death and disability globally and affects approximately half of all individuals over their lifetimes[140]. CVD has increased in developing countries, and by the year 2020, 80% of the global CVD mortality is predicted to occur in low- and middle-income countries[188]; (2) world population is threatened by increasing obesity, sedentary lifestyles, and diabetes mellitus rates[187]. If these conditions are added to increased BP, primary intervention strategies directed towards community rather than individuals become of more therapeutic value; (3) nine to ten potentially modifiable risk factors account for 90% of the attributable risk for myocardial infarction and stroke, with similar estimates in all major regions of the world[189,190]; and (4) the prevalence of low risk factor burden is on the increase. In the US it was only 4.4% during 1971-1975, 10.5% during 1988-1994, and 7.5% during 1999-2004[191].

In addition to the above reasons, it has been shown that monodrug therapeutic intervention in PHTN has yielded mixed results, with some researchers have shown benefits[184] while others have not[185]. It seems that the existence of comorbidities determines how a prehypertensive subject is likely to respond to pharmacological intervention[192]. Hence, the authors propose to consider including prehypertensives in future clinical trial of the Polypill to investigate how much benefit they may gain by multidrug therapeutic intervention.

### Clinical evidence for the polypill effectiveness

Two randomized, placebo-controlled trials investigated the therapeutic effect of the polypill. The first was conducted in 2011[193]. It was an international randomised placebo-controlled trial of a four-component combination pill ("polypill") in people with raised cardiovascular risk (over 7.5%, determined by the Framingham risk) using data on age, gender, BP, total cholesterol, HDL cholesterol, diabetes status, and cigarette smoking status. It contained aspirin 75 mg, lisinopril 10 mg, hydrochlorothiazide 12.5 mg, and simvastatin 20 mg or to placebo. The drug combination was associated with a 9.9-mmHg drop in SBP and a 0.8-mmol/L reduction in LDL cholesterol over a 12-wk treatment period.

The second clinical trial[194] studied a polypill contained amlodipine 2.5 mg, losartan 25 mg, hydrochlorothiazide 12.5 mg and simvastatin 40 mg; but contained no aspirin. The pill was given for 12 wk. The treatment showed reductions mean systolic (17.9 mmHg) and DBP (9.8 mmHg) and LDL blood level was reduced by 1.4 mmol/L.

## CONCLUSION

PHTN is a major health challenge that requires extra-attention. The "challenge" resides in finding the answer to "how/what" should be the intervention strategy (or strategies) that may best reduce its health impact.

In the search for a "strategy" to intervene in prehypertension, a number of considerations may be noteworthy and can be summarized as follows: (1) the rationale behind therapeutic intervention in hypertensive, and, indeed, prehypertensive subjects is to prevent (or delay progression of) cardiovascular events and mortality caused by these conditions. Yet, it is equally accepted that presence of other comorbidities such as diabetes mellitus, obesity, dyslipidemia, *etc.* in addition to ethnic, age and gender differences should also be accounted for when an intervention strategy considered; (2) the term PHTN is based on "defining" HTN itself, which is established on a 20-mmHg per brackets. Yet, BP is confounded by many factors such as circadian rhythms, food intake, stress, exercise, emotional state etc. leading to "variable BP variability"[137,195]; (3) based on the above two points, it is plausible to suggest that, categorizing and staging of subjects on basis of BP alone may need to be re-considered. It may be more clinically useful to contain factors, together, that cause BP variability to "stage" BP levels as well as to calculate cardiovascular risk factors. Such, may produce new terminologies or new definitions of PHTN and HTN. Consequently, an intervention strategy may not be "one-size-fits-all", and may necessitate more than one intervention. Different strategies (or combination thereof) may be considered. For example, males may require a different strategy from females since differences between genders have been reported in overt HTN[196,197]. Similarly, children PB progression differs from that of adults[198] and, thus may need a different intervention strategy. Furthermore, different ethnicities have shown different patterns in both progression of their BP as well as response to therapy and, hence, they may need different intervention strategies[199-202]; (4) the first-line treatment for prehypertensives should be based on adoption of a healthy lifestyle, especially if there are other associated risk factors such as obesity, dyslipidemia, pre-diabetes or diabetes, excessive alcohol intake, sedentary lifestyle and smoking[203] as well as salt-intake restriction[152]. It is desirable if TLCs would be adopted by government and NGOs and may be "enforced" as a "policy" that is directed (in a way similar to the antismoking campaign) towards changing community behavior; and (5) if pharmacologic means will be used, such should not be confined to drugs affecting RAS, other drugs may be investigated to ascertain whether it is the mere reduction in BP that is benefitting prehypertensives or other effects.

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