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EDITORIAL

# *World Journal of Hypertension*: A new bench mark in the hypertension world

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## Abstract

This is the first issue of the *World Journal of Hypertension* (*WJH*), a bimonthly peer-reviewed, online, open-access (OA) journal. The *WJH* will emphasize basic and clinical research about hypertension. As the OA model provides free, full-text articles in PDF and other formats for experts and the public without registration, the *WJH* enhances the speed of propagation and communication of scientific research results. As Editor-in-Chief of the *WJH*, I and the other members of the editorial board wish to share new ideas and knowledge about basic, clinical research and epidemiology in hypertension. We believe that you will find the *WJH* as an important journal in which to publish your excellent works.



**Key words:** Hypertension; Basic; Clinical; Peer-reviewed; Open-access; Journal

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**Figure 1 Editor-in-Chief of the *World Journal of Hypertension*.** Ryuichi Morishita, MD, PhD, Professor, Department of Clinical Gene Therapy, School of Medicine, Osaka University 2-2 Yamada-oka, Suita 565-0871, Japan.

## INTRODUCTION

This is the first issue of the *World Journal of Hypertension* (*World J Hypertens*, *WJH*, online ISSN 2220-3168, DOI: 10.5494), a bimonthly peer-reviewed, online, open-access (OA) journal. The preparatory work of the journal was initiated on January 23, 2011 and now the *WJH* Editorial Board has now been established and consists of 101 distinguished experts from 28 countries. I am Ryuichi Morishita, Professor at Osaka University, Graduate School, Osaka, Japan (Figure 1), and now the editor-in-chief of the *WJH*. It is my great honor to introduce the *WJH* as a new forum for exchanging thoughts and experiences about basic and clinical research to solve the problems of hypertension. I would like to say "Congratulations" to the publisher, members of the editorial board of the journal, all the authors and readers for the launch of the *WJH*!

Hypertension is still the leading risk factor for morbidity and mortality throughout the world[1], although numerous anti-hypertensive drugs have been developed. Unfortunately, the pathogenesis of essential hypertension is still an enigma, although the genetic approach has highlighted the large contribution of genetic factors to hypertension. From the viewpoint of medical therapy, the guidelines for hypertension treatment from various countries have now focused on co-existing cardiovascular

risk factors and subclinical end organ damage, in addition to optimal blood pressure control. However, there are still numerous questions about when and how to treat hypertensive patients in special circumstances. With this regard, the *WJH* offers a new cutting edge in the hypertension world.

Among the many journals related to hypertension, why choose the *WJH*? The role of academic journals is to exhibit the scientific levels of a country, a university, a center, a department and even a scientist, and to build an important bridge for communication between scientists and the public. As we all know, the significance of the publication of scientific articles lies, not only in disseminating and communicating innovative scientific achievements and academic views, and promoting the application of scientific achievements, but also in formally recognizing the "priority" and "copyright" of innovative achievements published, as well as evaluating research performance and academic levels. So, to realize these desired attributes of the *WJH* and create a well-recognized journal, the *WJH* is an OA journal and readers around the world can immediately download and read, free of charge, high-quality, peer-reviewed articles from the *WJH* official website.

## SCOPE

*WJH* aims to rapidly report new theories, methods and techniques for prevention, diagnosis, treatment, rehabilitation and nursing in the field of hypertension. The *WJH* covers topics concerning atherosclerosis, atrial fibrillation, blood pressure measurement, cerebrovascular diseases, clinical aspects and trials for hypertension, community cardiovascular practice, diabetes, hypertension education programs, endocrine hypertension, epidemiology of hypertension and metabolic disorders, experimental and renal hypertension, hypertension-related heart failure, hemodynamics, imaging procedures, implementation of guidelines, lifestyle changes, microcirculation, molecular biology, neural mechanisms, new therapeutic developments, obesity and metabolic syndrome, organ damage, pharmacoeconomics, public health, renin-angiotensin system, sleep apnea, therapeutics and clinical pharmacology, traditional medicine, and integrated Chinese and Western medicine. The journal also publishes original articles and reviews that report the results of hypertension-related applied and basic research in fields such as immunology, physiopathology, cell biology, pharmacology and medical genetics.

## CONTENTS OF PEER REVIEW

In order to guarantee the quality of articles published in the journal, *WJH* usually invites three experts to comment on the submitted papers. The contents of peer review include: (1) whether the contents of the manuscript are of great importance and novelty; (2) whether the experiment is complete and described clearly; (3) whether the discussion and conclusion are justified; (4) whether the citations of references are necessary and reasonable; and (5) whether the presentation and use of tables and figures are correct and complete.

## COLUNNS

The columns in the issues of the *WJH* will include: (1) Editorial: to introduce and comment on the substantial advance and its importance in the fast-developing areas; (2) Frontier: to review the most representative achievements and comment on the current research status in the important fields and propose directions for the future research; (3) Topic Highlight: this column consists of three formats, including (A) 10 invited review articles on a hot topic, (B) a commentary on common issues of this hot topic, and (C) a commentary on the 10 individual articles; (4) Observation: to update the development of old and new questions, highlight unsolved problems and provide strategies on how to solve the questions; (5) Guidelines for Clinical Practice: to provide guidelines for clinical diagnosis and treatment; (6) Review: to systematically review the most representative progress and unsolved problems in the major scientific disciplines, comment on the current research status and make suggestions on the future work; (7) Original Articles: to originally report innovative and valuable findings in hypertension; (8) Brief Articles: to briefly report novel and innovative findings in hypertension; (9) Case Report: to report a rare or typical case; (10) Letters to the Editor: to discuss and make reply to the contributions published in the *WJH* or to introduce and comment on a controversial issue of general interest; (11) Book Reviews: to introduce and comment on quality monographs of hypertension; and (12) Guidelines: to introduce consensuses and guidelines reached by international and national academic authorities worldwide on research in hypertension.

The mission of the *WJH* is to foster excellence in hypertension research, for the prevention of cardiovascular diseases and stroke and the improvement of the management of hypertension. If you have not yet submitted to the *WJH*, now is the time to join. Together with the excellent editorial board members, I look forward to serving the readers of the *WJH* and to working with you over the next few years so that the objectives of the *WJH* will be successfully achieved.

So, if you want to share any new ideas, any basic research or any clinical experiences in hypertension, the *WJH* is happy to provide a space for you!

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EDITORIAL

# Manidipine: A different dihydropyridine

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## Abstract

Blood pressure (BP) plays an important role in the development and progression of cardiovascular disease. Moreover, hypertensive patients often have additional cardiovascular risk factors. Despite the abundance of antihypertensive drug categories, satisfactory BP regulation is often difficult to achieve. A major cause of this difficulty to properly manage BP is the less than optimal adherence of subjects to treatment. This is often due to the various adverse effects of the antihypertensive drugs. Calcium channel blockers (CCB) have an established efficacy for reducing BP. However, their side effect of peripheral edema is often a cause for the discontinuation of treatment. Manidipine holds some unique properties differentiating it from the rest of the CCB class. It has a better safety profile with a lower incidence of peripheral edema. Moreover, there are indications that manidipine holds additional beneficial attributes, such as improvement of renal function and decrease of insulin resistance.



**Key words:** Manidipine; Hypertension; Calcium channel blockers; Peripheral edema; Renal function; Insulin resistance

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Rizos CV, Elisaf MS. Manidipine: A different dihydropyridine. *World J Hypertens* 2011; 1(1): 3-6 Available from: URL: http://www.wjgnet.com/2220-3168/full/v1/i1/3.htm DOI: http://dx.doi.org/10.5494/wjh.v1.i1.3

## INTRODUCTION

Hypertension is one of the key factors for cardiovascular disease (CVD) development and progression. The prevalence of hypertensive patients is continuously increasing[1]. Hypertensive subjects often have additional CVD risk factors, such as hyperlipidemia, impaired glucose metabolism and renal impairment, leading to an increased rate of CVD morbidity and mortality[2]. Therefore, a comprehensive management of both hypertension as well as concomitant CVD risk factors is critical when treating hypertensive patients.

There are various categories of antihypertensive drugs. However, despite the plethora of blood pressure (BP) lowering agents, satisfactory control of hypertension is often difficult to achieve. This is in part due to the adverse effects that the various antihypertensive drugs have, leading patients to discontinue treatment. Among antihypertensive drugs, calcium channel blockers (CCBs) have an established efficacy of BP reduction. A common adverse effect and often cause for the poor adherence to treatment with CCBs is peripheral edema.

Dihydropyridines CCBs act by blocking calcium channels, predominantly L-type channels, thus blocking the entry of $Ca^{2+}$ into cells. As a result, CCBs cause vascular smooth muscle relaxation and thus vasodilation. However, despite the same basic mechanism of action and the similar chemical structure (Figure 1), the effects of dihydropyridines CCBs are differentiated among the same class[3]. Indeed, the different pharmacokinetic profile (e.g. the elimination half-life, the extended release mechanism

of some formulations and the lipophilicity of the different molecules) can lead to diverse effects of different CCBs regarding BP, heart rate and left ventricular mass.

An interesting CCB in the category of dihydropyridines is manidipine. Manidipine holds a number of traits that make it unique among dihydropyridines CCBs (Figure 2). It has a better safety profile, thus improving adherence to treatment. Moreover, its promising pleiotropic effects beyond BP lowering make it an attractive option for hypertensive subjects with concomitant CVD risk factors.

## SAFETY PROFILE

Among the most common adverse effects of CCBs is peripheral edema, which is dose related[4]. CCBs preferentially dilate the precapillary arterioles without a commensurate dilation of the postcapillary venules[5]. Moreover, the CCB-mediated decrease of BP leads to the triggering of the baroreflex-induced stimulation of the sympathetic nervous system[6]. In turn, this activation of the sympathetic nervous system leads to the constriction of postcapillary venules. As a result, an increase of pressure gradient in the capillary level occurs, which together with the hydrostatic pressure lead to the formation of peripheral edema. However, manidipine has shown a smaller degree of sympathetic nervous system activation. Indeed, when compared with other CCBs, manidipine is associated with lower levels of plasma norepinephrine[7]. As a result, manidipine has been shown to have a smaller incidence of peripheral edema among CCBs[8,9]. Therefore, this favorable safety profile can improve adherence to treatment and thus provide better BP control.

## RENAL FUNCTION

Hypertension plays a critical role in the development and progression of renal disease[10]. Older dihydropyridines CCBs have not shown beneficial effects on renal function[11]. On the contrary, some studies have shown a decline of renal function after treatment with some CCBs[12]. There are 2 types of calcium channels: L-type and T-type. L-type calcium channels are predominantly found on afferent renal arterioles while T-type are predominantly found on efferent renal arterioles[13]. Older dihydropyridines CCBs preferentially act on L-type calcium channels. As a result, a vasodilation predominantly of the afferent glomerular arterioles is achieved with older CCBs. Therefore, no reduction in glomerular pressure is achieved and renal capillary pressure autoregulation is impaired, thus negatively affecting renal function. On the other hand, manidipine acts by blocking both L- and T-type calcium channels[14]. Consequently, a vasodilation of both afferent and efferent glomerular arterioles is achieved. As a result, manidipine improves glomerular capillary pressure and preserves renal capillary pressure autoregulation, thus favorably affecting renal function beyond BP lowering[13]. Indeed, various studies have shown the renoprotective effects and reduction of urinary albumin excretion with manidipine treatment[15,16]. Moreover, manidipine has been shown to be equally effective with enalapril (an angiotensin-converting enzyme inhibitor which has established renoprotective effects) regarding the progression of renal disease[17].

## METABOLIC AND CARDIOVASCULAR EFFECTS

An able percent of hypertensive patients have additional CVD risk factors such as dyslipidemia and impaired glucose homeostasis[18]. Some antihypertensive drug categories, such as diuretics and β-blockers, have an overall unfavorable effect on lipid profile and insulin resistance[19]. On the other hand, CCBs have been shown not to significantly alter lipid levels or glucose homeostasis[20]. Manidipine has also been shown to have a neutral effect on lipids[21]. However, a beneficial effect on insulin resistance has been shown with manidipine treatment[21]. Indeed, a reduction of insulin resistance has been observed with manidipine in both non-diabetic and type 2 diabetic patients[22,23]. This favorable effect of manidipine may be linked to the drug's capacity to partially activate the peroxisome proliferator activated receptor-γ (PPARγ)[21]. PPARγ modify the expression of numerous metabolic related genes and play a major role in glucose metabolism. The effect of manidipine to activate PPARγ is about two-thirds of that of pioglitazone, a full PPARγ activator[21]. This partial activation of PPARγ contributes to the avoidance of side effects commonly associated with thiazolidinediones treatment. Indeed, telmisartan, which is a partial PPARγ activator, has been shown to have a beneficial effect on insulin resistance without sharing the usual side effects of thiazolidinediones[24]. Moreover, an increase of adiponectin levels (which are inversely associated with the development of insulin resistance and metabolic syndrome) has been observed with manidipine[15].

Furthermore, manidipine has been shown to have an effect on cardiac function and remodeling. Indeed, a decrease of left ventricular mass[25,26] (an important CVD risk factor[27]) has been shown with manidipine treatment. Moreover, in an experimental study in rats, manidipine was associated with cardioprotective effects against heart ischemia - reperfusion injury[28]. In addition, manidipine has been shown to improve impaired coronary circulation while reducing left ventricular and vascular hypertrophy in hypertensive rats[29].

## CONCLUSION

Manidipine is a unique dihydropyridine CCB with established efficacy in BP reduction. In addition, manidipine holds some unique traits which differentiate it from the rest of the CCB class. Indeed, manidipine has a better safety profile with a lower prevalence of peripheral edema. This property can lead to a better adherence to

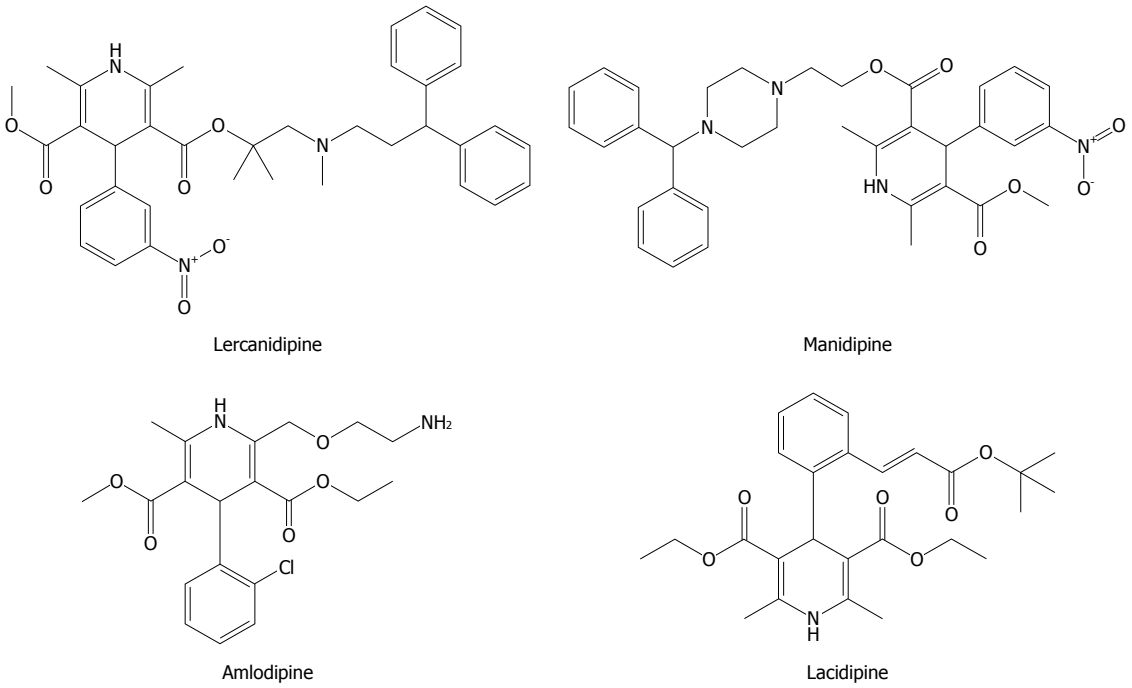


**Figure 1 Chemical structure of dihydropyridines calcium channel blockers.**

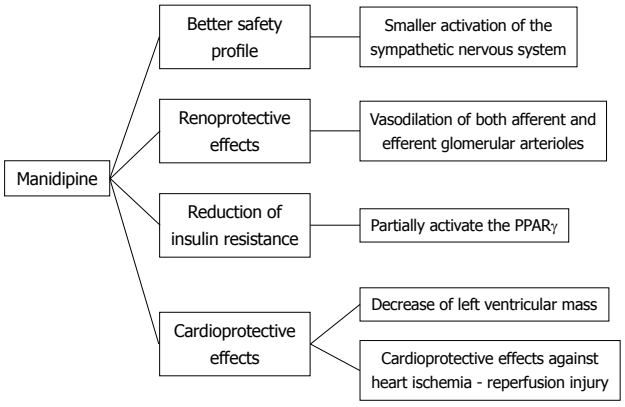


**Figure 2 Traits of manidipine.** PPARγ: Peroxisome proliferator activated receptor-γ.

treatment and therefore a better regulation of BP. Furthermore, the drug's ability to dilate both efferent and afferent renal arterioles contributes to the overall beneficial effects of manidipine on renal function. In addition, the capacity of manidipine to partially activate PPARγ contributes to the improvement of insulin resistance, which is often found in hypertensive subjects.

These pleiotropic effects of manidipine make it an attractive option for a more comprehensive management of hypertensive patients with the coexistence of additional CVD risk factors. Of note, it is unclear whether these pleiotropic effects of manidipine induce beneficial effects regardless of the antihypertensive effect. Moreover, promising results have been obtained when using manidipine in combination with angiotensin-converting enzyme inhibitors, such as dalapril in patients requiring a greater reduction of BP. Indeed, the manidipine/dalapril combination provided a better antihypertensive effect than monotherapy, together with a lower percentage of peripheral edema prevalence than manidipine alone[30,31].

However, these pleiotropic effects of manidipine only provide indications of possible benefits to be expected with treatment. Large clinical trials with hard clinical endpoints are needed in order to evaluate whether these pleiotropic effects are actually translated to clinical benefit.

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OBSERVATION

# Arterial hypertension, cerebrovascular diseases and dementia

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**Key words:** Arterial hypertension; Acute stroke; Cerebrovascular disease; Vascular dementia; Alzheimer's disease

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## Abstract

Arterial hypertension (AH) is the most relevant risk factor for acute cerebrovascular disease in general. However, the prevalence of AH is not the same for the different stroke subtypes and is particularly high in lacunar infarcts and atherothrombotic stroke, low in infarcts of unusual cause and undetermined origin, and intermediate in cardioembolic stroke. This risk factor has also been related to vascular dementia and Alzheimer's disease and their pathological manifestations (senile plaques, neurofibrillary tangles, hippocampal atrophy). The mechanisms linking AH to Alzheimer's disease remain to be elucidated but some recent studies showed that white matter lesions seen on cerebral magnetic resonance imaging appear to be a good marker of this association. Hypertension-associated pathological changes in the brain and its vasculature include vascular remodelling and impaired cerebral autoregulation like hypoperfusion, ischemia and hypoxia, which may initiate the pathological process of Alzheimer's disease and the expression of dementia. Therefore, prompt diagnosis and adequate control of hypertension and different vascular risk factors are the rational basis for a more effective strategy in the secondary prevention of cerebrovascular disease and dementia.



## INTRODUCTION

Stroke after heart disease and cancer is the third commonest cause of death in industrialized countries and accounts for more than 50% of all neurological hospital admissions to adult wards. Hypertension was found in 52% of patients with ischemic stroke included in The Sagrat Cor Hospital of Barcelona Stroke registry and constituted, as in other stroke registries, the most relevant risk factor for acute cerebrovascular disease in general as well as when acute cerebrovascular events are divided into ischemic stroke and hemorrhagic stroke[1].

## HYPERTENSION IN DIFFERENT STROKE SUBTYPES

Although hypertension is extensively recognised as a major cardiovascular risk factor, the prevalence of hypertension is not the same for the different stroke subtypes[1-3]. In our experience, the prevalence of hypertension is particularly high in lacunar infarcts (71.6%) and atherothrombotic stroke (66.1%), low in infarcts of unusual cause (27.2%) and undetermined origin (18.2%), and intermediate in cardioembolic stroke (49.4%) (Table 1)[1]. In the Athens Stroke registry, the most frequent risk factors in atherothrombotic stroke were hypertension (73%),

**Table 1 Arterial hypertension and other cardiovascular risk factors according to the ischemic stroke subtype in the Sagrat Cor Hospital of Barcelona Stroke Registry *n* (%)**

| Variable | Atherothrombotic (*n* = 770) | Lacunar (*n* = 733) | Cardioembolic (*n* = 763) | Undetermined etiology (*n* = 324) | Unusual cause (*n* = 114) |
|---|---|---|---|---|---|
| Hypertension | 509 (66.1)[d] | 525 (71.6)[d] | 377 (49.4)[d] | 59 (18.2)[d] | 31 (27.2)[d] |
| Atrial fibrillation | 120 (15.6)[d] | 81 (11.1)[d] | 573 (75.1)[d] | 25 (7.7)[d] | 8 (7.0)[d] |
| Diabetes mellitus | 242 (31.4)[d] | 218 (29.7)[d] | 142 (18.6)[b] | 24 (7.4)[d] | 6 (5.3)[d] |
| Hyperlipidemia | 164 (21.3)[d] | 166 (22.6)[d] | 88 (11.5)[d] | 52 (16.0)[d] | 10 (8.8) |
| Previous cerebral infarction | 164 (21.3)[a] | 117 (16.0) | 146 (19.1) | 31 (9.6)[d] | 10 (8.8)[b] |
| Ischemic heart disease | 150 (19.5)[a] | 104 (14.2) | 163 (21.4)[d] | 14 (4.3)[d] | 4 (3.5)[d] |
| Transient ischemic attack | 116 (15.1)[b] | 80 (10.9) | 73 (9.6)[a] | 37 (11.4) | 11 (9.6) |
| Smoking (> 20 cigarettes/d) | 87 (11.3)[a] | 86 (11.7)[d] | 28 (3.7)[d] | 41 (12.7)[d] | 18 (6.9) |
| COPD | 74 (9.6) | 61 (8.3) | 62 (8.1) | 20 (6.2) | 6 (5.3) |
| Peripheral arterial disease | 100 (13.0)[b] | 57 (7.8) | 50 (6.6) | 3 (0.9)[b] | 4 (3.5)[b] |
| Valve heart disease | 11 (1.4)[d] | 21 (2.9)[d] | 130 (17.0)[d] | 6 (1.9)[b] | 6 (5.3) |
| Congestive heart failure | 43 (5.6) | 24 (3.3)[b] | 72 (9.4)[d] | 8 (2.5)[b] | 1 (0.9)[a] |
| Obesity | 36 (4.7) | 47 (6.4)[d] | 17 (2.2)[b] | 13 (4.0) | 5 (4.4) |
| Oral anticoagulants | 18 (2.3)[a] | 7 (1)[d] | 63 (8.3)[d] | 2 (0.6)[d] | 4 (3.5) |
| Alcohol abuse (> 80 g/d) | 26 (3.4)[a] | 21 (2.9) | 5 (0.7)[a] | 10 (3.1) | 4 (3.5) |
| Chronic liver disease | 17 (2.2) | 15 (2.1) | 15 (2.0) | 10 (3.1) | 0 |
| Previous cerebral hemorrhage | 9 (1.2) | 9 (1.2) | 7 (0.9) | 6 (1.9) | 1 (0.9) |

[a]$P < 0.05$, [b]$P < 0.01$, [d]$P < 0.001$. COPD: Chronic obstructive pulmonary disease.

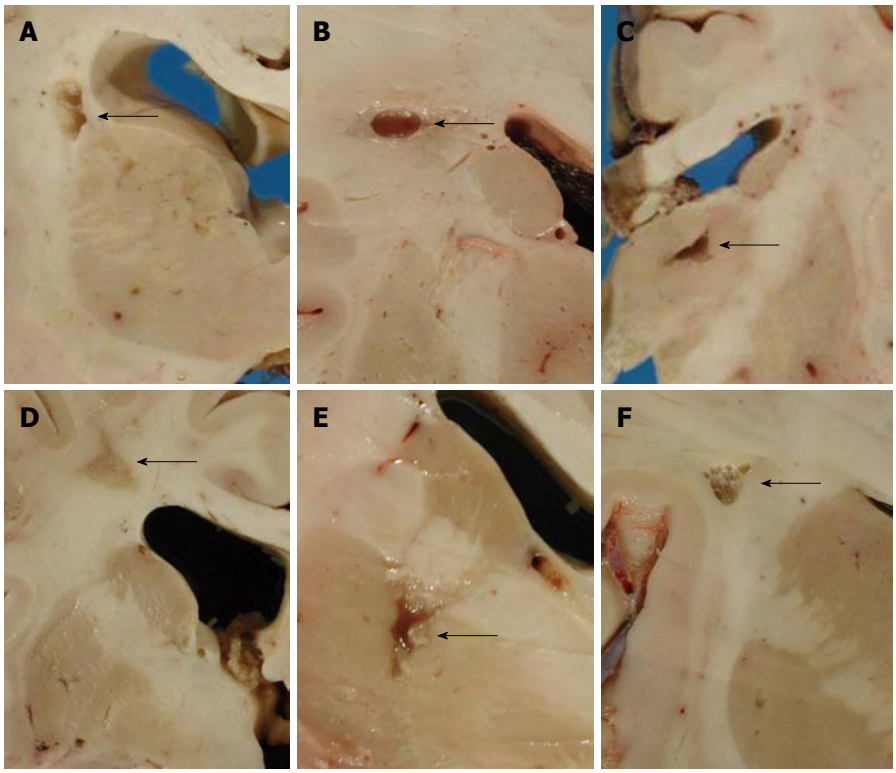


**Figure 1 Lacunar infarcts (arrows) in semi oval centre (A, B, D, F), thalamus (C) and putamen (E).** Figure provided courtesy of Isidre Ferrer (University of Barcelona, Catalonia, Spain).

smoking (51%) and dyslipidemia (46%)[4], whereas in the Ege Stroke registry, hypertension (70%), diabetes mellitus (45%) and dyslipidemia (35%) were the most common[5]. These findings reveal that hypertension does not constitute the main risk factor for all ischemic stroke subtypes. Hypertension is simultaneously a risk factor (for atherosclerosis) and a cause of lipohyalinosis associated with lacunar infarct (Figure 1).

On the other hand, high blood pressure may aggravate atherosclerosis and induce complex pathological changes in arteries and arterioles. As a consequence, hypertension is a precursor of large-artery disease and hypertensive small-vessel disease, such as lipohyalinosis, which is one of the most common causes of lacunar infarction[1,6-8]. In a recent clinical study, hypertensive patients with ischemic stroke have different clinical features than non-hyper-

tensive patients[1]. Lacunar syndrome, female gender and previous cerebral infarction were independent variables associated with hypertensive ischemic stroke[1].

## HYPERTENSION IN DEMENTIA

Hypertension is also a risk factor for ischemic white matter lesions, microbleeds, general atherosclerosis, myocardial infarction and cardiovascular diseases, and often clusters with other vascular risk factors, including diabetes mellitus, obesity and hypercholesterolemia. These risk factors have also been related to Alzheimer's disease[9] and their pathological manifestations (senile plaques, neurofibrillary tangles, hippocampal atrophy)[10]. The mechanisms linking hypertension to Alzheimer's disease remain to be elucidated but some recent studies showed that white matter lesions seen on cerebral magnetic resonance imaging appear to be a good marker of this association[11]. In terms of the pathophysiology of hypertensive brain damage, several hypothesis have been developed, such as hypertension may promote a pre-existing subclinical Alzheimer's disease, hypertension could determine neurobiological alterations (such as β-amyloid accumulation) resulting in neuropathological damage and, finally, age and cerebrovascular risk factors may act together to cause cerebral vascular degeneration, mitochondrial disruption, reduced glucose oxidation and reduced ATP synthesis. The consequences of these alterations are neuronal death and dementia[10-12]. Hypertension-associated pathological changes in the brain and its vasculature include vascular remodelling and impaired cerebral autoregulation like hypoperfusion, ischemia and hypoxia, which may initiate the pathological process of Alzheimer's disease and the expression of dementia[9].

## CONCLUSION

Management of hypertension is equally effective in reducing the risk of stroke in women and men. In addition, recurrent stroke has been shown to be more frequent among hypertensive patients than among non-hypertensive patients[13-16]. Therefore, prompt diagnosis and adequate control of hypertension and different vascular risk factors are the rational basis for a more effective strategy in the secondary prevention of cerebrovascular disease and dementia.

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GUIDELINES FOR CLINICAL PRACTICE

# Genome-wide association studies of hypertension: Achievements, difficulties and strategies

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## Abstract

Estimated from family studies, the heritability of hypertension ranges from 31% to 68%. Linkage studies and candidate gene association studies were once widely used to investigate the genetic mechanisms of hypertension. However, results from these studies could only explain 1%-2% heritability. With the technological advances and subsequently the accomplishment of the Human Genome Project, genome-wide association studies (GWA studies) have been applied to find genome-wide significant signals for many common diseases. Current GWA studies of hypertension have identified dozens of hypertension or blood pressure associated variants. However, different GWA study identified different variants and the results could hardly be replicated in other studies. Therefore, a debate took place on whether GWA studies will unlock the genetic basis of hypertension and whether we shall continue throwing millions of dollars on GWA studies. This review gives a short introduction to the history of genetic study on hypertension and summarizes the current findings for GWA studies of hypertension or blood pressure. Finally, we will discuss that debate and try to find alternative strategies and technologies that may hold a greater chance to make progress in understanding the genetic risk factors of hypertension and blood pressure regulation.



**Key words:** Hypertension; Genome-wide association study; Achievement; Difficulty; Strategy

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## INTRODUCTION

Genetic and epidemiological data have revealed that hypertension is a typical complex disease which arises from the interaction of polygenetic and environmental factors. For decades, scientists and cardiologists have known that the hypertensive traits are highly heritable. Estimated from family studies, the heritability of hypertension ranged from 31% to 68%[1,2]. Thereafter, multiple twin

studies showed that the heritability exceeded 50%, which indicated that more than half of the blood pressure variation could be attributed to genetic effects[3,4].

Family-based linkage studies were once widely used to investigate the genetic mechanisms of hypertension. They were quite successful in identifying the "hypertension causal gene"[5], but these genetic variants were not associated with hypertension in the general population[1]. Following this, many candidate gene-based and genome-wide linkage scans have been performed but none of these studies offered convincing results[6,7]. The main difficulty in identifying hypertension or blood pressure (HT/BP) associated genes is the low power of linkage study for variants with modest effects[8]. To compensate for the defect of linkage study, candidate gene association studies on HT/BP have been widely used. Hundreds of candidate genes have been examined, especially for genes involved in the rennin-angiotensin-aldosterone system and renal sodium transport system[9-11]. However, still not much progress has been made in candidate gene approach for hypertension and/or blood pressure.

## ACHIEVEMENT

With the technological advances and subsequently the accomplishment of the Human Genome Project, we are able to genotype 1 million single nucleotide polymorphisms (SNPs) at a reasonable cost. Genome-wide association studies (GWA studies) have been applied to find genome-wide significant signals for many common diseases[12]. The GWA studies represent the first unbiased survey of disease-predisposition variants in the genome. Hypertension was one of the first diseases to be studied by GWA study. The first large collaborative GWA study for hypertension was completed by the Wellcome Trust Case Control Consortium and the results were published in 2007[13]. However, none of the SNPs passed the threshold of genome-wide significance established at $P < 10^{7}$ in this study. At least twelve further GWA studies for HT/BP have been published since then[14-25] (for details see review by Ehret[1]). Two large-scale meta-analyses of GWA studies for HT/BP were published in 2009[17,19]. These were CHARGE BP consortium and Global BP Gen consortium, each of which analyzed 2.5 million genetic markers in about 30 000 individuals. Among all the GWA studies on hypertension, only these two studies on blood traits have identified genome-wide significant loci and could be replicated in other studies. However, only one SNP reached the genome-wide significance for hypertension and several SNPs for systolic blood pressure and diastolic blood pressure. Moreover, these implicated that SNPs had only minor effects on blood pressure (less than 1 mmHg) and accounted for no more than 0.2% of the overall blood pressure variation in the study population[26]. GWA study can be used to make a bright future for indentifying the genetic mechanisms of hypertension, which ultimately would be useful for early intervention for susceptible people and individual patient management. However, after 13 GWA studies, the results are quite disappointing.

## CONTROVERSY

Can GWA studies unlock the genetic basis of hypertension? Shall we continue throwing millions of dollars on GWA studies? Or shall we shift the research strategies and technologies that may hold a greater chance to make progress in understanding the genetic risk factors of hypertension? Recently, "Hypertension" published a debate that took place in an annual meeting in May 2010. The pro side representatives described the success of recent work, including 13 SNPs associated with HT/BP at $P < 5 \times 10^{-8}$. They also suggested a way forward, including resequencing using next generation sequencing technologies to aid fine mapping and the identification of causal variants, even bigger meta-analyses and developing appropriate functional studies to take way from GWA studies and related methodologies to useful clinical applications[27]. In the controversy, the con side representatives contended that GWA studies have failed in hypertension studies. Only 13 associated SNPs were found and few of them could be successfully replicated in follow-up studies. They suggested that research efforts and dollars should be shifted to other strategies and technologies that may hold a greater chance in advancing our understanding of the genetic factors that influence population variation in blood pressure and risk for hypertension[26].

## STRATEGY

Despite the different opinions, we still have to admit that the findings of GWA studies are an encouraging step in hypertension genetics because they open the way for subsequent investigations. It is also believed that one of the biggest gains from GWA studies is the expansion of the pathophysiology of hypertension. As in most cases, genes and regions identified are novel and fill critical gaps in our current knowledge. Moreover, a common non-coding SNP discovered might have a small effect, but the underlying gene/protein/pathway might become a very important target. Therefore, we should reconsider the research strategies according to the problems we have met.

Firstly, more homogeneous samples should be involved in GWA studies. Linkage study and the candidate gene approach have failed because of their low power to indentify variants with modest effects. Given the effective sizes observed and the number of tests performed, the power is still low, even in a GWA study with 30 000 individuals[1]. The International Consortium for Blood Pressure is organizing and will combine all of the cohorts from the Global BPgen and CHARGE with some additional cohorts and present data from > 70 000 participants[28]. Large-scale cohorts to study blood pressure traits in nonwhite populations (such as the Korean Association Resource, Chinese Han GeneID) are under way. Further meta-analysis with larger sample size would be

more widely used for the evaluation of the evidence.

Secondly, more ethnic populations should be considered in future studies. Our group have selected dozens of "hypertension-associated SNPs" from the above mentioned GWA studies and completed the replication study in the Han Chinese population but only one or two SNPs could be replicated in our own study (data not shown). It suggests that ethnic difference might be a great challenge in GWA studies. Several different ethnic populations have been examined in GWA studies but it has mostly focused on Europeans. This is mainly due to the well prepared European origin samples but it is also a great challenge to study Africans because of the complex recombination. Among 13 studies, only one was done on the Han Chinese population[24]. In 2009, Chinese Ministry of Science and Technology launched an 863 project of GWA study to identify the association between variants and hypertension in the Han Chinese (http://program.most.gov.cn/htmledit/UploadFile/20090310112521187.doc). To our knowledge, Hong Kong researchers are also carrying out GWA study in the Han Chinese. The more ethnic populations we study, the more useful information we get.

Thirdly, discoveries from GWA studies are inherently limited to common variants as a result of microarray design. Thus, rare variants (minor allele frequency < 5%) might be a more important source of "missing" heritability[29]. A good example of the potential role of rare variants in the pathogenesis of hypertension is found in Framingham Cohort study performed by Lifton and colleagues[29] in which they sequenced 3 genes and found 1 of every 64 subjects in the study carrying a mutation with potential function in 1 of these 3 genes. If more genes are sequenced in many thousands of people, it would not be surprising that more rare variants would be identified. For low allele frequency, the sample size should be carefully considered before we get reliable variants, and customized microarray should be used in later GWA studies. Thanks to quick advances in high-throughput DNA sequencing tools and analytic strategies, it appears that comprehensive searches for rare variants are becoming more feasible[30]. Thus, next-generation sequencing might take the part of GWA studies in future studies, which have been proved to be more successful in unlocking the genetics of hypertension[26].

Fourthly, recent genome-wide significant variants are often merely tag but without direct information on their functions. Classical cell-line reporter assays for *in-vitro* examination of the cis-regulatory effect of SNPs were usually used in the times of candidate gene approach; however, its throughput could not meet the needs now. Bioinformatics methods provide a chance to identify regulatory function of thousands of variants. Tang and colleagues developed the mixed linear model approach to examine the variance of genetic expression in the HapMap lymphoblast cell lines[31]. A simple extension to include fixed effects due to SNP genotypes within a window of certain distance into the model will demonstrate if particular candidate SNPs have a cis-effect on gene expression. Fine mapping sequencing or custom-made microarray approaches, together with ChIP-on-chip technology, will be widely used in future studies, not only to get a better estimate of the real effects on phenotype, but also to translate these signals to biological functions and clinical applications.

Finally, hypertension and blood pressure have been considered complex genetic traits since the classic work of Pickering and colleagues[32]. Before the era of GWA studies, epidemiological studies have found dozens of risk factors, such as smoking, alcohol abuse, excessive salt intake, obesity, mental stress, *etc*. It is widely believed that gene-environment interactions play an important role in the pathogenesis of hypertension but it is not currently possible to quantify them. The participants in recent GWA studies are mainly from well-organized cohorts (Global BPgen and CHARGE), which means the epidemiology data are available. With the development of statistical methods for evaluation of gene-environment interaction, more missing inheritability will be found.

## CONCLUSION

GWA study for the first time permits us to study most common variants in the human genome. Application of this technology to BP/HT traits has identified dozens of associated variants and contributed to a better understanding of BP regulation. However, current limitations of GWA studies impede the further findings and, thus, research strategies should be changed. Taking into consideration the populations, samples size, rare SNPs, functional study and gene-environmental interaction, the investigations will help us better understand the genetic basis of hypertension and blood pressure regulation, with potential benefits for prediction, early intervention, diagnosis and treatment.

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REVIEW

# Hypertension in children and adolescents

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## Abstract

Pediatric hypertension (HTN) has become the focus of interest recently due to its increasing prevalence. This is mainly related to the increase in childhood obesity, although the current evidence suggests that other lifestyle factors, apart from obesity, contribute to high blood pressure (BP) in childhood. Traditionally, office BP measurements by the physician have been the cornerstone for the assessment of HTN in children. However, since the white coat and masked HTN phenomena are not rare in childhood, out-of-office BP measurements have significantly improved the accurate diagnosis of HTN and decision making. Ambulatory BP monitoring is regarded as indispensable for the evaluation of pediatric HTN, providing details not only for the staging for HTN, but also for the study of other ambulatory BP patterns. It should be pointed out that HTN in children and adolescents is associated with target-organ damage which is significant in terms of cardiovascular risk. The current knowledge, outlined in the present review, is expected to help in early and accurate diagnosis as well as in the management of HTN in children and adolescents.



**Key words:** Hypertension; Blood pressure; Diagnosis; Children; Adolescents

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## INTRODUCTION

In the last two decades, our knowledge about childhood hypertension (HTN) has substantially increased. It is now recognized that pediatric HTN, particularly among adolescents, is not as uncommon as previously believed and in most cases represents early onset of essential rather than secondary HTN[1-4]. Moreover, HTN in children is related to preclinical target-organ damage such as left ventricular hypertrophy, microalbuminuria and increased carotid vascular thickness, thus conferring an increased cardiovascular risk in adulthood[5-8]. Out-of-office blood pressure (BP) measurements, especially ambulatory BP monitoring, have significantly helped in accurate diagnosis of HTN in childhood[9]. Current guidelines on BP assessment in children and adolescents are widely available, especially among pediatricians and primary care providers, helping them in screening, diagnostic and therapeutic interventions in children with high BP[10,11].

## EPIDEMIOLOGY AND RISK FACTORS

Several studies in Europe and US have shown the prevalence of high BP in children and adolescents to be at about 1%-4%[1-4]. Ethnic differences, as well as differences in protocols and methodology used to assess BP, account for the inconsistency in the findings worldwide. HTN in children aged < 6 years is usually secondary but in higher age categories (especially > 12 years) essential HTN is the rule[10,11].

Recent studies show increasing trends of average BP

in children and adolescents[12,13]. In particular, data from the US National Health and Nutrition Examination Surveys showed that after age, race/ethnicity and sex standardization, systolic and diastolic BPs were respectively 1.4 and 3.3 mmHg higher in 1999-2000 compared with 1988-1994[12].

The reported increase in childhood HTN may have important implications in terms of cardiovascular health. Longitudinal cohort studies have shown that BP tracks from childhood to adulthood, and that high BP in childhood confers a high risk of HTN in adulthood, thus supporting the need for early identification of high-risk individuals[14].

A consistent finding in most of the aforementioned studies is the strong association between obesity and high BP. In particular, the obesity epidemic appears to be the major contributor of the increasing trends in childhood HTN. However, apart from obesity, other factors such as adverse lifestyle and dietary habits appear to be associated with increased BP levels in children and adolescents[15,16]. In particular, lack of physical activity and sedentary behavior, as well as dietary salt intake have been associated with increased BP in children independent of body composition[15,16].

## DIAGNOSIS OF HTN IN CHILDREN AND ADOLESCENTS

Diagnosis of HTN depends on accurate BP measurements. However, there is a fundamental difference in the diagnosis of HTN in children compared to adults. Recommendations for adults are derived from observational and interventional large, long-term outcome studies with hard endpoints of morbidity and mortality. Such studies in children and adolescents are largely unfeasible since, not only are the cardiovascular events far in the future (making follow-up very difficult), but also because multiple confounding factors will infiltrate and influence the cardiovascular risk through time, thereby diluting the net effect of treatment-induced BP decline. Therefore, there is a lack of evidence about threshold BP values for intervention and BP goals in children and adolescents. As a result, many of the classifications and recommendations are based on statistical considerations and assumptions or on extrapolation from evidence obtained in adults.

Measurement of BP by a physician in the office using a mercury sphygmomanometer has been the cornerstone for diagnosis of HTN[10]. In 2004, the US National High BP Education Program Working Group on High BP in Children and Adolescents published normalcy tables for office BP on the basis of a large database of more than 70 000 children and adolescents[10]. These tables provide the 50th, 90th, 95th and 99th BP percentiles for each year of age and according to height percentiles (based on the growth charts of the Center for Disease Control and Prevention) for boys and girls[10]. BP measurement is performed with a mercury sphygmomanometer or, if not available, a calibrated aneroid device and the auscultatory method, with first (K1) and fifth (K5) Korotkoff sounds defining systolic and diastolic BP respectively[10]. An appropriate size of cuff is very important and the length of the bladder in the cuff should cover 80%-100% of the individual's arm circumference. It is recommended that all children > 3 years old seen in a medical setting should have their BP measured.

The recent European Society of Hypertension (ESH) recommendations for the management of high BP in children and adolescents also adopted the US Task Force normalcy tables, since these were derived from a large dataset[11]. According to the 2004 US Task Force and the ESH guidelines, the 90th and 95th office BP percentiles for gender, age and height are used to diagnose normotension, pre-HTN and HTN on the basis of average systolic and diastolic BP levels on at least three separate occasions[10]. Measurements obtained by oscillometric devices that exceed the 90th percentile should be repeated by auscultation. It should be pointed out that oscillometric monitors used in children should be validated specifically in the pediatric population. As in adults, adolescents with BP levels over 120/80 mmHg should be considered as pre-hypertensives even if their BP is below than the 90th percentile. Both the ESH and the US guidelines categorize hypertensives into stage 1 (95th-99th centile + 5 mmHg) and 2 (> 99th centile + 5 mmHg)[10,11].

## WHITE COAT AND MASKED HTN IN CHILDREN

White coat HTN is characterized by office BP higher than the 95th percentile while outside the clinical setting BP is normal. The first report on the white coat phenomenon in children came from a study published in 1991 in 159 children with a positive family history of HTN, 44% of whom were classified as white-coat hypertensives[17]. Subsequent studies reported a prevalence of white-coat HTN ranging from 10% to 60% according to the methodology used and the population studied (healthy, referred for elevated BP or other)[18-20]. The relationship of white-coat HTN with the presence of target-organ damage in children and adolescents seems to be somewhat unclear. More specifically, children with white-coat HTN have been reported to have higher values of left ventricular mass index[21,22]. On the other hand, Stabouli *et al*[23] reported that white-coat hypertensives tended to have higher left ventricular mass index compared with normotensives, but the difference was not statistically significant.

Masked HTN refers to high BP values outside the office with normal values in the clinical setting. The first study reporting on masked HTN was conducted in Japan, in 136 normotensive (on the basis of office BP) individuals aged 6-25 years old, showing that the prevalence of masked HTN was 11%[24]. A larger Spanish study by Lurbe *et al*[25] including 592 children and adolescents aged 6-18 years old, showed that 90.4% of the children were normotensive, 0.8% hypertensive, 1.2% had white-coat

HTN and 7.6% had masked HTN. Interestingly, 8.8% of subjects with masked HTN developed sustained HTN during the study follow-up, and subjects with persistent masked HTN had increased prevalence of left ventricular hypertrophy compared to normotensives[25]. A more recent study in Greece using ambulatory BP monitoring in 85 children and adolescents referred for elevated BP, reported that the prevalence of HTN was 25%, of white-coat HTN 13% and of masked HTN 9.4%[23]. Therefore, in children and adolescents referred for elevated BP, masked HTN and white-coat HTN are common phenomena[26]. The data for target-organ damage in children with masked HTN are in agreement with findings in adults that showed masked HTN to be associated with increased left ventricular mass[25].

## OUT-OF-OFFICE BP MEASUREMENTS AND ASSOCIATION WITH TARGET-ORGAN DAMAGE

The conventional measurement of BP by the physician in the office or clinic for the assessment of HTN has certain disadvantages, such as the aforementioned white coat and masked HTN phenomena, the observer prejudice and bias and the regression to the mean. Out-of-office BP measurements have been increasingly used in children and adolescents for the accurate assessment of HTN.

### *Ambulatory BP monitoring*

Ambulatory BP monitoring in children and adolescents was first adopted in the early 1990s in the context of the research field, but recently it has been increasingly used for clinical purposes[27]. In recent guidelines, ambulatory BP is regarded as an indispensable method for the evaluation of pediatric HTN[10,11].

The normalcy tables for ambulatory BP measurements, based on data from 1141 children and adolescents, provide the 90th and 95th percentiles (proposed threshold for normotension and HTN respectively) according to age and height and have been endorsed by both the American and the European guidelines[10,11,28,29].

Several studies have examined the relationship of ambulatory BP with subclinical target-organ damage in children and adolescents. Among several indices of preclinical target-organ damage, left ventricular hypertrophy appears to be the most extensively studied index due to the wide availability of echocardiography. Several studies have reported the prevalence of left ventricular hypertrophy in hypertensive young individuals ranging from 10% to 46% and have shown an independent association of ambulatory BP monitoring parameters with left ventricular mass index[30-33]. Also, ambulatory BP in children has been associated with other indices of subclinical target-organ damage such as carotid intima media thickness, glomerular filtration rate and carotid-femoral pulse wave velocity[8,34,35].

According to the published guidelines, the diagnosis of ambulatory HTN is defined as average 24-h, daytime or nighttime systolic and/or diastolic ambulatory BP $\geqslant$ 95th percentile for gender and height or age[11,29]. However, apart from the diagnosis of HTN and the detection of white-coat and masked HTN, ambulatory BP monitoring is useful in the identification of several ambulatory BP patterns in children and adolescents. More specifically, isolated nocturnal HTN and abnormal nocturnal dipping, which are often seen in subjects with secondary HTN or chronic diseases such as diabetes, can be detected only by using 24-h ambulatory BP monitoring[29]. Furthermore, ambulatory BP monitoring is of paramount importance in the evaluation of antihypertensive treatment effects and particularly in the assessment of refractory HTN, the evaluation of BP control in children with target-organ damage and in the recognition of symptomatic hypotensive episodes[29]. Lastly, ambulatory BP monitoring can provide information on arterial stiffness (ambulatory arterial stiffness index)[35].

### *Home BP monitoring*

In children, the available evidence on the usefulness of home BP monitoring is less than for ambulatory monitoring. Studies have shown that home BP monitoring is feasible in the pediatric population in terms of acquiring a decent number of measurements, with or without (in older children and adolescents) the parent's assistance[36]. As in the case of adults, home BP monitoring in children might be useful in the diagnosis of HTN and allows the detection of the white coat and the masked HTN phenomena[37]. Only one study, the Arsakeion study in Greece performed in 778 healthy children and adolescents, has attempted to provide normalcy tables which have been endorsed by the recent ESH guidelines[36]. Interestingly, home BP has been associated with subclinical target-organ damage in hypertensive children as closely as ambulatory BP[38].

## DIAGNOSTIC EVALUATION

The confirmation of HTN should be combined with a thorough history and physical examination[10,11]. Past medical history should focus on possible definable causes of hypertension. Questions should be asked about prior hospitalizations, trauma, urinary tract infections, snoring and other sleep problems. Many drugs, especially over the counter and illicit drugs, can increase BP. Family history is also very important. Physical examination should include assessment of the child's body mass index and measurement of BP in both arms and a leg. It should also assess signs and symptoms suggesting renal disease (gross hematuria, edema, fatigue, epigastric/flank bruit, palpable kidneys), heart disease (chest pain, exertional dyspnea, palpitations) and diseases of other organ systems (e.g. endocrinological, rheumatological).

Routine laboratory investigation in children with high BP should include full blood count, plasma sodium, potassium, calcium, urea, creatinine, fasting plasma glucose

and lipids, as well as urinalysis. Organ damage evaluation should include heart, great vessels, kidney, central nervous system and retina. As mentioned before, left ventricular hypertrophy is the main target-organ damage evident in children with HTN and echocardiography is necessary in all these cases. More specialized tests for secondary causes should be restricted in children aged < 12 years, as well as in children with symptomatic or stage 2 HTN. It should be pointed out that the diagnostic evaluation for secondary HTN should always follow confirmation with ambulatory BP monitoring.

## MANAGEMENT OF HTN IN CHILDREN AND ADOLESCENTS

Non-pharmacological interventions should be the initial step in the management of HTN in children and adolescents[10,11,39]. Weight loss, aerobic physical activity and dietary modifications have been shown to be associated with a decrease in BP levels[10,11,39]. Given that obesity is closely associated with HTN, measures aiming at weight reduction and maintenance of ideal body weight are of paramount importance. A recent meta-analysis showed that a modest reduction in salt intake was associated with significant reductions in systolic and diastolic BP[40]. Although sodium restriction is difficult to achieve in this age range, avoiding processed foods, paying attention to sodium content (on the food labels) and avoiding table salt are useful practices[39]. Apart from sodium restriction, a diet rich in fruits and vegetables and poor in saturated fat, sweetened beverages and fast foods may be efficient in terms of BP reduction. In fact, dietary approaches, such as DASH (Dietary Approaches to Stop Hypertension), have been shown to effectively decrease BP levels in younger subjects[41]. In addition, everyday aerobic physical activity of moderate to vigorous intensity, in combination with a reduction in sedentary activities, is a wise recommendation.

Pharmacological therapy should be initiated when patients have symptomatic HTN, hypertensive target organ damage, secondary HTN or diabetes mellitus type 1 or 2 at the time of presentation, as well as in cases of sustained HTN despite the implementation of non-pharmacological measures[11]. It should be pointed out that non-pharmacological therapy should be continued after starting pharmacological therapy.

Concerning BP targets, in general BP should be below the 90th age-sex and height specific percentile (except in subjects with chronic kidney disease where BP should be below the 75th percentile in children without proteinuria and below the 50th percentile in cases of proteinuria)[11].

As in the case of adults, five classes of drugs are suitable for BP control in children and adolescents, including angiotensin converting enzyme inhibitors, angiotensin receptor blockers, β-blockers, calcium channel blockers and diuretics[11]. It should be noted that the indications for the use of these drugs in children are derived from short-term trials and that there are no trials with cardiovascular end points or trials comparing different classes. Thus, guidelines about the use of specific drugs in children are not solid and treatment should be individualized, in some cases directed from underlying pathophysiological mechanisms and extrapolation of data from adults[39,42,43]. Angiotensin converting enzyme inhibitors and angiotensin receptor blockers are preferred in children with diabetes and microalbuminuria or proteinuric renal disease. Treatment should begin with low doses of each agent and titrated on the basis of BP response and potential adverse effects. In children and adolescents, a significant response can be achieved even with the lowest doses of drugs. Subjects who do not respond to their initial drug may be switched to another category or require combination therapy with different classes of drugs. Monitoring should include assessment of BP levels and potential target-organ damage as well as evaluation of compliance.

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## Events Calendar 2011

January 11, 2012
Supporting the Challenge: Implementing the new NICE Hypertension Guidelines in Primary Care
BHS/PCCS/Takeda Workshop for Nurses & Pharmacists
Bristol, United Kingdom

February 8, 2012
BHS Hypertension & Cardiovascular Risk Spring Update for Nurses
Aberdeen Royal Infirmary,
Aberdeen, United Kingdom

February 10-12, 2012
Malaysian Society of Hypertension 9th Annual Scientific Meeting 2012
Kuala Lumpur, Malaysian

February 24, 2012
BHS Hypertension Masterclass
NICE Hypertension Guidelines: Essential Hypertension and Pregnancy
The Møller Centre, Churchill College,
Cambridge, United Kingdom

February 25- 28, 2012
Serbian Society of Hypertension 3rd International Meeting 2012
Belgrade, Serbia

March 3-5, 2012
South African Hypertension Society 17th Biennial Congress 2012
Cape Town, South Africa

March 14-18, 2012
9th Mediterranean Meeting on Hypertension and Atherosclerosis
Turkish Society of Hypertension and Atherosclerosis
Antalya, Turkey

March 22-25, 2012
2nd Latin America Congress on Controversies to Consensus in Diabetes, Obesity and Hypertension 2012
Rio de Janeiro, Brazil

April 11-13, 2012
ICDHLSP 2012: International Conference on Diabetes, Hypertension, Lipids and Stroke Prevention
Venice, Italy

April 26 - 29, 2012
22nd Scientific Meeting of the European Society of Hypertension
Excel Centre,
London, United Kingdom

May 19 - 22, 2012
2012 American Society of Hypertension Annual Scientific Meeting & Exposition
Hilton New York,
NY, United States

June 21-24, 2012
10th International Pulmonary Hypertension Conference and Scientific Sessions 2012
Orlando,
FL, United States

July 9-12, 2012
3rd International Congress on Abdominal Obesity 2012
Quebec City, Canada

July 9-12, 2012
International Society for the Study of Hypertension in Pregnancy 18th World Congress 2012
Geneva, Switzerland

September 30 to October 4, 2012
Hypertension Sydney 2012
Sydney Convention and Exhibition Centre,
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The biggest advantage of the OA model is that it provides free, full-text articles in PDF and other formats for experts and the public without registration, which eliminates the obstacle that traditional journals possess and usually delays the speed of the propagation and communication of scientific research results. The open access model has been proven to be a true approach that may achieve the ultimate goal of the journals, i.e. the maximization of the value to the readers, authors and society.

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*WJH* aims to report rapidly new theories, methods and techniques for prevention, diagnosis, treatment, rehabilitation and nursing in the field of hypertension. *WJH* covers topics concerning atherosclerosis, atrial fibrillation, blood pressure measurement, cerebrovascular diseases, clinical aspects and trials for hypertension, community cardiovascular practice, diabetes, hypertension education programs, endocrine hypertension, epidemiology of hypertension and metabolic disorders, experimental hypertension, renal hypertension; and hypertension-related heart failure, hemodynamics, imaging procedures, implementation of guidelines, lifestyle changes, microcirculation, molecular biology, neural mechanisms, new therapeutic development, obesity and metabolic syndrome, organ damage, pharmacoeconomics, public health, renin-angiotensin system, sleep apnea, therapeutics and clinical pharmacology, traditional medicine, and integrated Chinese and Western medicine. The journal also publishes original articles and reviews that report the results of hypertension-related applied and basic research in fields such as immunology, physiopathology, cell biology, pharmacology, medical genetics, and pharmacology of Chinese herbs.

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**Journals**

*English journal article (list all authors and include the PMID where applicable)*

1 **Jung EM**, Clevert DA, Schreyer AG, Schmitt S, Rennert J, Kubale R, Feuerbach S, Jung F. Evaluation of quantitative contrast harmonic imaging to assess malignancy of liver tumors: A prospective controlled two-center study. *World J Gastroenterol* 2007; **13**: 6356-6364 [PMID: 18081224 DOI: 10.3748/wjg.13.6356]

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2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

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3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

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5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

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6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

**Books**

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10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

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11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

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12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

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13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

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14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

**Patent** (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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Write as mean ± SD or mean ± SE.

### *Statistical expression*

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as $\chi^2$ (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

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