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Hypertension Journal is a peer-reviewed journal which highlights epidemiology, health implications and cardiovascular risk from hypertension in India/South-Asia. Hypertension is much more common than diabetes. It is vastly under diagnosed and poorly treated in India/South-Asia. There are excellent therapeutic options to treat hypertension, but the available resources are not fully utilized by doctors therefore neglecting this disorder. The journal will hereby promote the significance of hypertension and the urgent need to bring it under control. The medical community should be educated on hypertension evaluation, diagnosis, workup and management simultaneously bringing up the literature, research, guidelines and scientific advances related to hypertension and its disorders. We are hereby starting a high-quality journal dedicated solely to hypertension and thus promoting the awareness, evaluation and effective management in India/South-Asia. Dr C Venkata S Ram is a world authority on hypertension with lifelong work (research, clinical and publications).

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Editorial

Preventing a Hypertension "Storm Surge" in Southeast Asia

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Hypertension (HTN) and cardiovascular disease (CVD) remain the top killer in most parts of the world,[1] and in the Philippines, they account for more than a quarter of all deaths.[2] Based on the mortality statistics released by the Philippine Statistics Authority, of the 582,183 deaths in 2016, around 164,524 were due to ischemic heart disease, cerebrovascular disease, and other HTN-related diseases.[3] Just like in most parts of the world, elevated blood pressure (BP) is the single most attributable cause of deaths in our country.[4]

Although in the more affluent countries in the region such as Singapore and Brunei, the prevalence of HTN is going down, comparable to that in other first-world or high-income countries, the prevalence in the low- and middle-income countries in Southeast Asia (SEA) is still on the rise.[5-7] In a region where strong tropical typhoons are a constant threat, an HTN "storm surge" looms over our heads.

The overall prevalence rate in the region continues to increase. Approximately more than 30% of adults in SEA have raised BP ≥140/90 mmHg. Almost 1.5 million deaths, comprising 9.4% of total deaths, are attributed to HTN yearly.[4,5,7]

Awareness remains a big problem in the region, and in several countries, the awareness level is still <50%, with a little over half of them on treatment. It still follows the global rule of halves in HTN. Just like in the rest of the world, control rates to BP levels below 140/90 mmHg still leave much to be desired.[4,5,7]

The long-term cardiovascular outlook is even made worse with the rising tide of type 2 diabetes mellitus (T2DM), as a frequent comorbidity of HTN in the region. HTN and T2DM coexist in 40–60% of individuals diagnosed with either of the two.[5,8] The presence of both diseases heightens the cardiovascular risk, making CVD as still the leading cause of deaths in several countries in the region.

It is truly unfortunate that despite all efforts by the government and the private sector, there is still an increase in the number of people dying from acute myocardial infarction, cerebrovascular accidents, and other HTN-related cardiovascular events in the past 10 years, compared to a few decades earlier.[2]

It is also quite alarming that Filipinos, similar to other Asians, are developing strokes and heart attacks at a relatively younger age compared to Caucasians, despite having a leaner body frame. One likely reason for this is still the dismally inadequate control of elevated BP in the country. In the Philippines, although the HTN awareness rate has somewhat improved with continuing public health education campaigns by an alliance of organizations organized by the Philippine Heart Association (PHA) and Philippine Society of HTN (PSH), only one of five hypertensive Filipinos have their BP reduced to target level of <140/90 mmHg.[2]

If we were to adopt the redefined BP threshold for HTN of <130/80 mmHg from the American College of Cardiology/American Heart Association (ACC/AHA),[9] the control rate is likely to be <10% and the prevalence to be close to 50% of adult Filipinos. Both the PHA and the PSH recommend still adhering to the old BP diagnostic cutoff of 140/90 mmHg or higher.

Many practicing physicians, particularly primary care physicians, rely on published treatment guidelines to help them in the diagnosis, evaluation, and treatment of their hypertensive patients. At least seven countries in SEA have published national HTN guidelines,[5] which have very similar recommendations to international guidelines such as the 2017 ACC/AHA guidelines and the 2018 European Society of Cardiology/European Society of HTN guidelines. Efforts have been made though to locally attune the guidelines, addressing local issues, and concerns.

One population-directed intervention which has shown reasonable success in some countries in the region is reduction of salt intake at the population level.[10,11] This could perhaps be our best bet to really curb the rising tide of HTN in the region.

A paper reviewing levels of sodium intake in six SEA countries (Indonesia, Malaysia, the Philippines, Singapore, Thailand, and Vietnam) showed that sodium intake in most

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SEA countries was higher than the World Health Organization recommendation of 2 g/day.[12] More studies are needed though to accurately estimate sodium intake using 24-h urinary sodium excretion, which remains the "gold standard." Offhand though, it is quite clear that the sources of the excess dietary sodium are the added sauces, condiments, and processed foods – including instant noodles and meals – which are quite popular in many countries in the region. There is no question that sustained consumer education is imperative to make population-directed salt reduction strategies effective.

There are barriers that need to be overcome to achieve better prevention and control of HTN in the region. Among these are cultural norms and traditional practices that encourage unhealthy behaviors and promote misconceptions about HTN, like believing that HTN only needs treatment when one has symptoms. There is also a lack of an enabling environment for healthy lifestyle practices, still high smoking rate despite the additional excise taxes imposed on tobacco products, inequities in health care with insufficient facilities, and resources for early detection and treatment, particularly in primary health-care facilities. Treatment adherence or long-term patient compliance is another major barrier which may be due to financial constraints, i.e., high out-of-pocket cost of treatment.[5,13,14]

It is heartening to note that majority of the countries in SEA are bolstering their health education campaigns to make the public more aware of the perils of HTN and are actively collaborating with global initiatives in this regard. One of these initiatives is the May Measurement Month (MMM) campaign of the International Society of HTN (ISH) since 2017.[4] It is an annual month-long global undertaking with more than 80 countries actively participating to raise awareness of HTN. The MMM campaign is intended to serve as a temporary expedient solution to the inadequate screening programs in many countries worldwide. The SEA region has been very active in this campaign, contributing significantly to the global pool, which has screened more than 1.2 million in 2017[4] and 1.5 million in 2018.[15]

Indeed, the professional and political will to control HTN and prevent its "storm surge" are well in place in most countries in the region. However, it may not be as easy as a walk in the park. The lofty goal of HTN prevention and control is a complex one, and only an effective multisectoral collaboration could achieve it in the foreseeable future.[5] Professional cardiovascular organizations, the rest of civil society, food manufacturers and outlets, the government, health officials, policymakers, and the most important stakeholders – the patients and their families – should work hand in hand to get their act together against this killer disease. The governments should increase allocation of financial and other resources for HTN and CVD control programs, particularly population-directed and primary health-care approaches, wherein high-risk hypertensive individuals are identified and prioritized for treatment.

There are no shortcuts to HTN prevention and control. A sustained awareness, treatment, and control programs encouraging positive health-seeking behavior in the population are imperative to get us to goal – and that is, to achieve the 25 by 25 vision[16] or aspiration of global cardiovascular organizations including the World Heart Federation and ISH. The vision aims for a 25% reduction in the prevalence of HTN and likewise reducing all HTN-related complications by the year 2025 in SEA and worldwide.

It may be a utopian goal, but nonetheless, still a goal worth pursuing if we wish to thwart the "storm surge," HTN is poised to cause the SEA region and the rest of the world in our lifetime.

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A Tribute

Prof. Ramon Abarquez Jr

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When Prof. Ramon F. Abarquez, Jr., MD, EFACC, FPCC, FPCP, CSPSH founded the Philippine Society of Hypertension (PSH) 26 years ago in 1993, he asked during the inaugural meeting of the Society: "Why do millions have to die due to hypertension-related complications when something could be done."

For the next 25 years, he nurtured the PSH to become one of the robust multispecialty societies involved in various hypertension researches and advocacies, inspiring likewise the establishment of a highly committed alliance of more than 20 medical organizations and governmental and non-governmental organizations collaborating in all advocacy programs on hypertension control in the country.

In 1996, he led the organization of the Asia Pacific Rim Hypertension Summit, inviting international experts on hypertension for a highly interactive discussion on how we could stem the tide of hypertension in the region. During the summit, the Asian PSH was born with Prof. Abarquez as one of its founding members and officers.

Last year on January 10, 2018, he passed away at the age of 89 leaving a sterling legacy as one of the icons in Cardiovascular Medicine, specifically in the field of hypertension, in the country and the Asia Pacific region.

He will always be remembered for his generosity in sharing his expertise, innovativeness in research, healthy lifestyle advocacy, and passion for academic and professional excellence.

Emeritus Professor

Even after his official retirement from the University of the Philippines College of Medicine (UPCM), Prof. Abarquez continued to give lectures to medical students and attend medical conferences on his wheelchair. He was given the title of emeritus professor by the college, but he remained active in the academe, in research activities and clinical practice. He was prolific in writing scholarly articles published in medical journals and in health and lifestyle (H&L) magazine, for which he wrote a regular column that his peers and students always looked forward to read for its rich information and insights.

With a sterling record as a UPCM faculty and scientist, Prof. Abarquez was elected academician of the Philippine National Academy of Science and Technology (NAST) in 1993. Academicians are distinguished members of the NAST – the highest recognition for Filipino scientists. They also serve as the highest scientific advisory body in the country. From their ranks are nominated, the National Scientists Dr. Abarquez was nominated for this distinguished title.

Peers recognize Dr. Abarquez's contribution to Philippine medicine. He provided clinical practice-changing insights with his pioneering researches, more than 200 of which have been published in international peer-reviewed journals. Of these, 27 papers received awards and recognition here and abroad.

"The best legacy a doctor can give is pioneering research outputs and advocacies perceived to be the first at that point in time," Prof. Abarquez wrote in one of his commentaries in H&L. He chaired the medical advisory board of the magazine and was one of its most diligent columnists who submitted articles way ahead of the deadline. Even when he was already confined in the hospital, he maintained his column and would patiently dictate his piece to his nurse.

Innovative Researches

As early as 1960, Prof. Abarquez's research works were already groundbreaking. His innovative research made possible the stress test or exercise electrocardiogram (ECG) test. As a cardiology research fellow then, he was funded and tasked by the New York Heart Association to develop a technique to record the ECG of a patient during exercise, which was not possible at that time. Despite initial setbacks, he persevered, and after more than a year of experimentation, he was able to design successfully the prototype of the stress test electrodes currently used worldwide.

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Prof. Abarquez's prototype produced a successful recording of the ECG during exercise. As senior author of this pioneering study, he presented an innovative research in a scientific meeting of the American Heart Association Convention in Florida, for which he was recognized by prominent international authorities in cardiovascular medicine.

It is no exaggeration to say that hundreds of millions of patients with ischemic heart disease from 1960 to the present have benefited and continue to benefit from Prof. Abarquez's innovative research early in his career. For this, he was given the Cultural Heritage Award by the Philippine government in 1963, after returning from training abroad.

Redefining Hypertension

In 1979, he pushed for the treatment of hypertension at a level of 140/90 mmHg, then considered by international expert bodies to be still normal. High blood pressure then was defined as 160/100 mmHg or higher, but he and his research team at the University of the Philippines, Philippine General Hospital, published a study showing that there were already abnormal changes in the heart and arteries of individuals with as low a level as 140/90 mmHg.

Prof. Abarquez also published the first paper showing that a certain class of drug, the calcium channel blockers, which was then being used only to control high blood pressure, could also be used for patients with myocardial ischemia.

His other notable researches and contribution to the science of medicine include:

a. Observational data suggesting that the addition of digitalis to antihypertensive agents can prevent left ventricular dysfunction in hypertensive patients, and improve survival in post-myocardial infarction cases;
b. The proposal to the World Health Organization Western Pacific Task Force to include the use of coconut products along with olive oil and fish oil in reducing coronary artery disease based on association studies;
c. Low total body potassium exists among diabetics and can be reflected in the ECG;
d. Primordial prevention of hypertension is an important proactive approach rather than mere reactive management;
e. The survival of Filipino patients following myocardial infarction is one of the lowest in the world.

Healthy Lifestyle Advocacy

Although Prof. Abarquez advocated adequate drug treatment for various heart ailments, he always emphasized the importance of healthy lifestyle changes, which, to him, should be the foundation of treatment of all cardiovascular diseases. This was at a time when many considered therapeutic lifestyle changes as difficult to sustain on the long term.

To promote this, he coined the catchy slogan "SEX-HDL," which stood for smoking cessation, exercise, control of high blood pressure, diabetes, and lipid abnormalities by means of a healthy diet and a physically active lifestyle. He emphasized that SEX-HDL should be a family affair, meaning parents should set the example to motivate their children to lead a healthy lifestyle.

Prof. Abarquez was past president of the Philippine Heart Association/Philippine College of Cardiology, Philippine College of Physicians and PSH.

The Philippine and Asia Pacific medical community will certainly miss Prof. Abarquez. He cast a giant shadow on the practice of medicine in the region. Although he is now gone, the legacy of his teachings, philosophy, and ideals will remain in the hearts and minds of everyone whose lives he has touched.

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Review Article

A Review on the Status of Hypertension in Six Southeast Asian Countries

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ABSTRACT

The need for better blood pressure (BP) control has been advocated for years with its high correlation to cardiovascular morbidity and mortality. The rise of hypertension (HTN) in several countries, particularly the Southeast Asian region, has caused the increased numbers of cerebrovascular and cardiovascular diseases. Several factors have been identified that led to the rise of HTN; namely, the aging population, a lower socioeconomic status, lower educational attainment, sedentary lifestyle, a high Western diet, increasing obesity, and certain ethnicity. Although countries, such as Singapore, have better control of BP levels, most of the countries in the region have low awareness and treatment control of HTN. It is only through population-based programs in controlling raised BP that has been proven successful in HTN control.

Key words: Cardiovascular disease, hypertension, prevalence, Southeast Asia

INTRODUCTION

Hypertension (HTN) is the most common chronic disease in both developed and developing countries and is a major public health concern affecting adults. It is the leading cause of mortality and disability-adjusted life year all over the world, causes more cardiovascular deaths than any other modifiable cardiovascular risk factors, and is the second only to smoking as a preventable cause of mortality.[1-2] In the United States, National Health and Nutrition Examination Survey of more than 23,000 subjects, more than 50% of deaths from chronic heart disease and stroke occurred among patients with elevated blood pressure (BP). Approximately 1 billion people were estimated to be hypertensive in 2000, and most of these identified to be hypertensive live in lower and middle-income countries.[3-4] There have been several measures done to control elevations in BP, and while in developed countries, the prevalence of HTN appears to be stabilizing, the rates in the Southeast Asian region continues to rise.

Southeast Asia is a subregion in Asia consisting of Thailand, Malaysia, Indonesia, the Philippines, Singapore, Vietnam, Laos, Cambodia, Myanmar, and East Timor. About a third of adults in the region have HTN and nearly 1.5 million deaths are attributed to HTN annually.[5] It represents an important public health issue, as this is partly due in part to absent or poor disease management, with rates of uncontrolled HTN as high as 70%.[6] This paper looks at the different status of HTN prevalence, awareness, and control strategy available in six countries in SEA.

Status of HTN in Malaysia

Malaysia has a multiethnic population of 30 million spread over 13 states and three federal territories.[7] It is a highly developing nation, and in line with modernization and a growing economy, several Malaysians have adopted new lifestyles, habits, and dietary patterns. In an analysis of three National Health and Morbidity Surveys (NHMS) conducted in 1996, 2006, and 2011, and a large-scale non-NHMS survey, there was a rising trend in the prevalence of HTN among adults more than 30 years old in the country.[8]

The latest prevalence of HTN was 43.5% in 2011. The surveys suggest that HTN is higher among the elderly, in men, those with lower educational attainment, and lower income level. HTN is a big problem among the elderly, with a prevalence peaking at 74% in the 65–69 age group. Between sexes, there was

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comparable prevalence though a slightly higher prevalence in men (33%) than in women (31%).[8] HTN prevalence is found to be increased by 12% among people with an income level of RM 400 or lower.[9] People living in the rural setting also has a higher prevalence of HTN compared to those living in the urban area.

What is improving in the management of HTN is the increasing awareness and control of BP. There was an 8% increase in the awareness between 1996 and 2011. Control of HTN improved overtime, with an increase of 37%. Men are more aware than women, but women had better control than men.[8]

Despite the increasing awareness and control of BP in Malaysia, the magnitude of HTN management needs additional attention. Strengthening screening for HTN in a primary care setting would be of immense value. Frequent health promotion and public health measures such as education on healthy lifestyle, particularly weight control, reduced salt intake, modification of eating habits, and increased physical activity would enhance measures in BP control.[8]

Status of HTN in Indonesia

Indonesia is the world's largest island and the fourth populous country in the world. The top three causes of mortality in the country are non-communicable diseases: Stroke, diabetes, and ischemic heart disease. HTN is the second only to cigarette smoking as the leading cause of cardiovascular disease (CVD) in Indonesia. The Indonesian Family Life Survey (IFLS) in 2007 identified that HTN has a prevalence of 47% in individuals 40 years and older. In the same survey, there is a diagnosis rate of 37% and only a quarter of the hypertensive population were given prescription medication.[10]

Another IFLS was conducted in 2015 with approximately 30,000 individuals aged 18 and above included in the survey.[11] Using the Joint National Commission 7[12] definition of HTN of more than 140/90 mmHg, the prevalence of HTN decreased to 33.4%, with more women being hypertensive (35%) compared to men. Among the hypertensives, 42% were diagnosed, with more women being diagnosed than men. More people dwelling in the urban setting were diagnosed compared to people living in the rural area. However, only about 11.5% were being treated with antihypertensive medications, and only 14% had their BP controlled to less than 140/90 mmHg. The prevalence of HTN also increases with age and is also prevalent in individuals with lower education. Other factors that may affect hypertensive Indonesians include sedentary lifestyle, body weight status, and psychosocial stress.

One problem facing the country is the low awareness of the disease, with less than half of the population in Indonesia is aware that they are hypertensive, and a minority are treated and controlled. Several factors come into play, such as age, lower education, lifestyle condition, and stress. Identifying these factors may guide public health programs and community-wide interventions which will effectively reduce BP levels in Indonesia.

These interventions should be effective, realistic, and affordable to deliver high-quality primary care treatment.[11]

Status of HTN in Vietnam

Vietnam is an emerging economy in the Western Pacific region and has been enjoying a rapidly growing success in transforming market forces. However, the downside of the economic growth is the changing of dietary patterns and lifestyle which led to an increase in the prevalence of atherosclerotic disease. HTN is now a major public health problem as it was found to have a high hospitalization rate and mortality in hospitalized patients diagnosed to be hypertensives.[13,14] Several factors were identified to cause these increasing trends in HTN such as poor lifestyle and a generally weak community-based health information system.

A national survey was conducted in 2012 to determine the prevalence of HTN in Vietnam which included 9823 participants. Results showed that the prevalence of HTN is 25.1%, with men being more hypertensive than women. Age is also a factor, with the numbers increasing with age. However, in hypertensives more than 65 years old, women have a higher number than men. Urban dwellers are more hypertensives than people living in the rural areas. Factors affecting HTN include family history of HTN, overweight and obesity, and having abdominal fat.[15]

Less than half of the hypertensives in the survey (48%) were aware that they have HTN. Unfortunately, only 29.6% being treated with antihypertensive medications, and only 10% have their BP reduced to <140/90 mmHg. Factors identified for the poor awareness of HTN include low educational level, people living in the urban area, and high family history of HTN.[13,15]

The increasing number plus the low rates of awareness and control have implications in the public health strategies of the country. There is a need to mandate a population-based strategy to lower the number of individuals with high BP. There is also a need to create a clinical strategy, so as to manage existing hypertensive individuals and lower the complications of elevated BP such as heart attack, heart failure, and strokes.

Status of HTN in Thailand

Cardiovascular diseases caused an estimated 145,000 deaths annually in Thailand,[16,17] and HTN is identified as the leading risk factor responsible for approximately half of the disease burden from CVD. HTN is highly prevalent and in the latest National Health Examination Survey in 2015, one of four adult Thais has HTN. Similar to the other Southeast Asian nations, there is low awareness of the disease. Of those aware of their BP levels, only 29% have their BP controlled to <140/90 mmHg.[18]

Identified risk factors of HTN among Thais include increasing age, obesity, and comorbidities. Among men, HTN is associated with physical inactivity, smoking, and fast food intake. In women, having a partner is associated with HTN.[18]

Due to the high prevalence but poor awareness of HTN in Thailand, the World Health Organization, United States Center for Disease Control and Thailand Ministry of Health decided to come together to strengthen HTN care in Thailand. Several

experts from the government, academe as well as physicians, nurses, and program managers attended a meeting in 2017 to discuss strategies in controlling BP. The program is called Global Hearts Initiative and commenced last 2018.[19]

Status of HTN in the Philippines

Cardiovascular disease is the leading cause of morbidity and mortality in the Philippines and elevated BP is identified to be one of the major risk factors. The prevalence of HTN in the country has been increasing. Several cross-sectional studies have shown that the numbers are steadily increasing; from 11% in 1992 to 25% in 2008.[20] The National Nutrition and Health Survey (NNHES) of the Food and Nutrition Research Institute conducted in 2012 indicated a small decline in the prevalence of individuals with HTN, about 22.3%. Unfortunately, the survey is based on a single visit BP measurement alone. The same survey also showed that the highest prevalence of HTN is found in the 70 years old and above age group, males have a higher rate of elevated BP, patients who live in the rural areas, and those who have high economic status.[20]

In a prospective, multistage, stratified, two-phase, nationwide survey published in 2007, the prevalence of HTN in 3901 participants was 21%. HTN prevalence would increase by 50% in individuals more than 50 years old. It is more common in the urban areas, particularly in Metro Manila, and is more common in the middle economic stature. Similar to the other countries in Southeast Asia, awareness and control are very low. Only 16% of those surveyed are aware of having elevated BP. Treatment control was seen in only 20% of the hypertensives. In the survey, Filipino patients were prescribed more with a beta-blocker, but compliance rate is higher if they are on an angiotensin receptor blocker.[21]

The island nation of the Philippines has 7101 islands and the geography has caused difficulty in the delivery of healthcare in the country. Government programs are being implemented to include treatment of non-communicable diseases. Recently, the Universal Health Care Act has been passed which guarantees equitable access to quality and affordable health-care services for all Filipinos.

Status of HTN in Singapore

In a developed country like Singapore, there is a declining prevalence of HTN, from 27.3% based on the Singapore National Health Survey in 1998 to a prevalence rate of 23.5% in 2010. This is attributed to the improvement of BP control, from less than half of the hypertensive population with <140/90 mmHg in 2004 to about 67% of the individuals with their BP controlled in 2010. More Singaporeans are also receiving treatment, 69.1% surveyed in 2010 are receiving treatment, compared to only 52.9% in 2004.[22]

However, similar to the other countries in Southeast Asia, Singapore is faced with an aging population. Individuals who are aged 60–69 years have 53.4% prevalence of HTN, compared to only 7.6% prevalence in aged 30–39 years. Singaporean men are slightly hypertensive than the women. Based on ethnicity, the Malays had the highest prevalence in HTN, compared to the Chinese and Indian ethnic groups living in the tiny island of Singapore. In a survey among the elderly population in Singapore, other factors affecting HTN treatment and control include education, housing type, body mass, and diabetes.[23]

Although there was improvement in the medical services in Singapore, there is a need to look into programs targeting the elderly and their primary health-care providers. Several campaigns should be undertaken by the government to improve awareness and manage HTN in this population subset. A government subsidized Integrated Screening Program should be promoted, with the use of non-invasive BP measurement for easy detection of hypertensive individuals. Primary prevention through lifestyle changes should also be a particular focus of the government programs. As the aging population in Singapore is increasing, these preventive measures should go hand in hand with the aggressive treatment in Singapore and would eventually reduce the untreated HTN population.[23]

Discussion

Several factors have been identified which can explain the increasing prevalence of HTN in the Southeast Asian region. Most of the countries have developing economies, and the improving wealth and technological advancement led to a more Western lifestyle. The urbanization made people more sedentary and adhered to an unhealthy diet. These factors led to increasing rates of overweight and obesity which increase the prevalence of HTN. The aging population in the region, such as Singapore, has increased the prevalence of HTN and should be looked at. Cigarette smoking was also identified to have a high prevalence in hypertensive patients in Southeast Asia. People who belong to a lower economic class and failed to reach a higher educational attainment have a higher prevalence of elevated BP, as seen in countries such as Vietnam and the Philippines. Ethnicity may also play a certain role in BP elevation, as seen in Singapore, as the Malays have a higher BP level compared to other ethnic groups.

Countries with better economies, such as Singapore and Malaysia, have shown improvement in awareness and treatment control of HTN. People have better access to health care and government programs are in place for primary prevention. However, there are countries in the region who lack health-care access; thus, we see poor adherence and treatment rates. There are steps being taken, such as the programs in Thailand, which may answer the poor treatment control in HTN.

National guidelines are also available in some of the countries in the region, such as in Singapore and Thailand. Majority of the countries also have public awareness campaigns on HTN. However, similar to the American and European policymakers, guidelines need to be updated, especially with the new data coming out for HTN. Management of HTN is complex and should be approached using a multisectoral collaboration. There

is a need for a strong leadership to execute all these programs, if we want to reduce the problem that is HTN.

Conclusion

HTN is an urgent public health problem, particularly in Southeast Asia. Factors, such as lifestyle changes, aging population, cigarette smoking, and poor economic status, may lead to worsening HTN and can hinder adherence and control. A multisectoral collaboration on population-based programs may be needed to lower the prevalence of HTN.

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Review Article

A Closer Look at the Latest United States and European Pediatric Hypertension Guidelines and its Impact on Local Practice

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Abstract

Background: For lack of the Philippine consensus on diagnosis, evaluation, and management of childhood and adolescent hypertension (HTN), local practice follows the United States (US) and European guidelines. **Aim:** The latest US and the European guidelines were examined for its potential benefits, limitations, and impact on local practice. **Results:** Essential differences and similarities between these two guidelines were recognized. Identified gaps include discrepancies in the diagnosis and classification of HTN among adolescents, including the age cutoff (13 vs. 16 years old). The applicability of the 24-h ambulatory blood pressure (BP) monitoring – although more superior in terms of BP information – is not practical at present. The European Society of HTN (ESH) recommendation for home BP monitoring is more feasible to implement. Adoption of the more rigorous screening and follow-up schedules of the American Academy of Pediatrics and the extensive diagnostic workup of the ESH guidelines are essential aspects useful to local practice. These strategies can minimize both over- and under-diagnosing pediatric HTN. The non-pharmacologic and pharmacologic treatment approaches of both guidelines are practical and feasible to implement. The optimal BP targets, especially those of high-risk populations to prevent excessive cardiovascular morbidity and mortality, are ideal. **Conclusion:** Due to the limitations of both guidelines in its applicability to local practice, the formulation of a country-specific BP consensus guideline is ideal. Modeling some parts of the recommendations in the screening, workup, and treatment that can contribute to best practice and outcomes is a goal.

Key words: Adolescents, american academy of pediatrics, european society of hypertension, filipino children, impact

Background

The tracking phenomenon of childhood hypertension (HTN) is widely recognized. Large population-based longitudinal studies showed that a hypertensive child would carry on to become a hypertensive adult.[1] Thus, early recognition and intervention while still at the pediatric age group will prevent these future adults from adding on to the burgeoning population of adult hypertensives at risk for devastating stroke, myocardial infarction, congestive heart failure, arrhythmia, and other cardiovascular events.

Over the years, new clinical knowledge, breakthroughs, and scientific evidence have made it difficult for physicians to thresh out crucial medical information necessary for everyday clinical decisions. Hence, clinical guidelines were formulated to assist practitioners in making more consistent and efficient judgments at the bedside and outpatient clinics. Clinical practice guidelines have increasingly become a standard part of clinical practice. These systematically developed recommendations developed into influencing rules of operation at the clinics, hospitals, and even health directives of insurers and government policymakers to standardize practice and improve clinical outcomes.

In the Philippines, there is no clinical practice guideline drafted for pediatric HTN. The American Academy of Pediatrics (AAP) and the European Society of HTN (ESH) guidelines have served as the references and the sole basis for the standard of care. From the time, the guideline updates were published

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in 2016 (ESH) and 2017 (AAP), scrutiny of its impact to our local population has never been made. In this review, potential benefits and limitations as applied to local practice are explored.

Screening and Diagnosis of Childhood and Adolescent HTN

Accumulation of new medical knowledge stimulated an update of the United States (US) and the European guidelines on pediatric HTN. In 2016, the ESH published its revised version of the guidelines on high blood pressure (BP) in children and adolescents from its first issued guidelines in 2009. Notable in the 2016 guideline is the revised definition of HTN in children 16 years and older. It also highlighted the significance of isolated systolic HTN in children, the importance of out-of-office and central BP measurement, newer risk factors for HTN, methods to assess for vascular phenotypes, clustering of cardiovascular risk factors, and treatment strategies.[2]

On the other hand, AAP released its guidelines for screening, diagnosis, and management of childhood and adolescent HTN in 2017, an update of the prior guidelines of the National Heart, Lung, and Blood Institute Fourth Report on High BP in Children in 2004. Significant changes from the fourth report include revised definitions of BP categories in alignment with the American Heart Association/American College of Cardiology guideline; new normative BP tables based on BPs from normal weight children; simplified screening table and a rigorous evidence-based methodology. It also emphasized the use of 24-h ambulatory BP monitoring (ABPM) in confirming the diagnosis of HTN. Included in the revision are recommendations for the performance of echocardiography and lower treatment goals for primary HTN as well as the ABPM goal for chronic kidney disease (CKD).[3]

Significant differences and similarities are prominent in each of the two guidelines. For instance, in the definition of HTN, the adults based its HTN definition on the cardiovascular morbidity and mortality associated with a certain level of BP, while the pediatric HTN BP definition is arbitrary. HTN is defined based on the normal distribution of BP in healthy children. Because the BP in children is influenced by sex and has been shown to increase with age and body size, interpretation of BP levels is dependent on sex, age, and height. In younger children then, there is no single BP level that can be utilized to define elevated BP. Both guidelines recognize this fact.

Moreover, both guidelines define normal BP in younger children as BP less than the 90th percentile. However, the age cutoff for adolescents differs for both guidelines. The AAP has set the cutoff at 13 years and older and 16 years and older as per ESH guidelines. For both guidelines, elevated BP is now defined by absolute values, for a seamless transition into the adult definition of HTN. The AAP guideline has introduced a new term for BP >90th percentile as "elevated BP" previously referred to as "pre-HTN" in the older guideline, and "high-normal" is the term used by the ESH guideline. Table 1 shows the other similarities and differences between AAP and ESH BP definition.

Correct identification of abnormal BP in children relies on BP tables obtained from normative values of a specific population. The new normative BP tables commissioned for the 2017 AAP clinical practice guidelines were based only on BP readings from ~50,000 multiethnic, normal weight children while the 2016 ESH guidelines have adapted the 2004 US normative data obtained from auscultatory clinic measurement generated from BP values in ~70,000 healthy children which included overweight and obese children.[2-4] Increasing numbers of ethnic-specific reference values, including from China and India, are published.[5,6] Other countries, including the Philippines, with no BP norms, consider the AAP as the international standard. The validity of its application to other ethnic populations is unclear.

A study in India revealed a consistently different pattern in comparison to the existing US reference. Three readings of BP taken by mercury sphygmomanometer and anthropometric data from 20,263 students aged 5–16 years have shown higher diastolic BP for both sexes than international standard across all age groups. For systolic BP values, although the difference appears to be minimal for boys, girls showed higher values than

Table 1: American Academy of Pediatrics and the European Society of Hypertension BP definitions for children and adolescents (1–18 years old)

BP categories and stages	AAP*		ESH**	
	For 1–12 years old (Percentile/mmHg)	≥13 years (Percentile/mmHg)	For 0–15 (Percentile/mmHg)	≥16 yearsW (Percentile/mmHg)
Normal	<90th	<120/<80	<90th	<130/85
Elevated/high-normal	≥90th–<95th or 120/80 mmHg to <95th (whichever is lower)	120–129/<80	≥90th–<95th	130–139/85–89
Hypertension	Not addressed	Not addressed	>95th	≥140/90
Stage 1	≥95th–<95th+12 mmHg or 130/80–139/89 mmHg (whichever is lower)	130–139/80–89	95th–99th+5 mmHg	140–159/90–99
Stage 2	≥95th+12 mmHg or ≥140/90 (whichever is lower)	≥140/90	>99th+5 mmHg	160–179/100–109
Isolated systolic hypertension	Not addressed	Not addressed	SBP≥95th and DBP<90th	≥140/<90

BP: Blood pressure, AAP: American Academy of Pediatrics, ESH: European Society of Hypertension, SBP: Systolic blood pressure, DBP: Diastolic blood pressure

the international standard.[5] Similarly, a comparative study demonstrated higher body mass-adjusted BP levels among South Asian children than White children in the US.[7] Inclusion of overweight and obese children in the norms adopted by the ESH guidelines likely biased normative BP values upward, leading to the underdiagnosis of HTN.

In the Philippines, several issues deemed to be essential in the application of these guidelines to local practice are identified. For instance, it does not include the BP norms of severely stunted children. From a 2011 national survey, excessive stunting, i.e., height below the 5th percentile is noted in 34% of Filipino children younger than 5 years old.[8] Looking at the AAP BP norms, the height cutoff was set at the 5th percentile. It is uncertain if the BP values of children at the 5th percentile are reflective of those below or equal to children with height third percentile. Second, we found a discrepancy in the definition of abnormal BP in both guidelines. To illustrate, a 5-year-old Filipino boy with height at the fifth percentile and a BP of 122/70 mmHg, by AAP definition, falls under the category of Stage 2 HTN and Stage 1 HTN by ESH definition.

Another example would be an adolescent 13-year-old male with a BP of 120/79. Under the AAP, he has elevated BP and a normal BP under the ESH guidelines. Third, many of the 95th percentile BPs for adolescents 16 and 17 years of age were well below the adult cutoff points for HTN. This difference would practically result in a hypertensive adolescent, becoming a normotensive at 18 years of age. These loopholes will then lead to underdiagnosis and missed opportunities for intensive screening, prevention, early diagnosis, and intervention. On the other hand, overdiagnosis will bring about needless and costly workups and unwarranted anxiety among pediatric patients and their caregivers. Due to these discrepancies, there is a need to establish country-specific BP norms that would account for the differences, explain, and cover the cardiovascular risks associated with ethnic predispositions to HTN.

The rigorous screening and follow-up schedules of the AAP guideline and the more extensive initial evaluation for hypertensive children and adolescents of the ESH guidelines are valuable and beneficial for local implementation. Special consideration is the country's unique geography. Most patients come from areas geographically remote from the hospital or clinic. Therefore, every physician encounter must be maximized. Once the diagnosis of HTN is confirmed, extensive workup must ensue to identify the etiology (since secondary HTN is more common in children) and treatment initiated early before sending the patients home. This way, dropouts will be avoided as it would be inconvenient and costly for the patients to return to complete the workup as well as start treatment.

Methods of BP Determination

The BP norms were derived from values obtained using a mercury sphygmomanometer combined with an inflated cuff and auscultation. To date, this method remains the gold standard for the measurement of BP in children. The ban on mercury spurred the use of automated oscillometric and aneroid devices as methods for BP determination. Both guidelines allow for its use provided that the device is appropriately calibrated for pediatric use. However, in cases of abnormal BP, it is recommended to confirm manually, i.e., by auscultation. Locally, the use of automated oscillometric BP machines is rare. Manual (auscultatory) BP determination using aneroid devices has widely replaced the mercury sphygmomanometer. The auscultatory method using an aneroid device is advantageous as it cancels out the confounding effect of the inherent differences in BP readings using these automated devices.[9] The AAP recommends the use of 24-h ABPM for all hypertensive children at diagnosis, children with elevated BP for 1 year and for those with high-risk conditions such as CKD, history of solid organ transplantation, prematurity, obesity, and diabetes; while the ESH recommends its use only at initiation of antihypertensive medication. ABPM is advantageous as it is more reflective of the circadian variability of BP. It can precisely capture white coat and masked HTN. However, it is not practical for local use at this time. Not many centers have the apparatus and the workforce to implement ABPM. Besides, there are no locally available normative values for the correct interpretation of ABPM results. The ESH recommends a more practical tool suitable for local practice, the home BP monitoring. Home BP monitoring is a useful adjunct to the diagnosis and treatment of children with HTN. The recommendation includes specific guidance on how to properly conduct home BP monitoring as well as normative data tailored explicitly to home BP monitoring. This approach allows for more practical application of the guidelines, as completing the required in-clinic BP measurement for HTN diagnosis can be a barrier for some patients and providers.

Management of Childhood and Adolescent HTN

Both guidelines are similar in the non-pharmacologic and pharmacologic approaches in the treatment of HTN. Emphasizing lifestyle modification is noteworthy. The ESH has a more specific weight loss recommendation, level, and duration of an activity. Both recommend the dietary approaches to stop HTN (DASH) diet. The DASH diet has been proven to work.[10] It is, however, challenging to implement the reason being, processed foods are cheaper compared to the prohibitive cost of meals included in the DASH diet.

Optimal BP targets, especially those with obesity, diabetes, CKD, and those who had solid organ transplantation, are reasonable and achievable. Good BP control has been shown to prevent the progression of CKD as well as minimize cardiovascular risks.[11,12]

Conclusion

BP tracking phenomenon in childhood HTN is widely recognized; thus, early recognition, diagnosis, and treatment can prevent future cardiovascular risks. Except for the derivation of BP norms and the discrepant HTN definitions in both the US

and European guidelines, most of the recommendations are essential models for drafting future country-specific pediatric HTN guidelines.

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Review Article

The Impact of the 2017 American College of Cardiology/American Heart Association and the 2018 European Society of Cardiology/European Society of Hypertension Guidelines on the Asian Population: Is it Time for Our Own Asian Hypertension Guidelines?

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Abstract

Hypertension (HTN) remains to be the single most important risk factor for the development of cardiovascular disease worldwide. Moreover, the global burden of disease is expected to rise even more in the coming years due to the obesity epidemic and the aging population. However, control rates of high blood pressure (BP) remain low. The American College of Cardiology/American Heart Association 2017 Guidelines and the European Society of Cardiology/European Society of HTN 2018 Guidelines have different thresholds and targets, with the US guideline "redefining" HTN to a new lower level, while the European guideline remains unchanged from its previous levels. There is now emphasis on proper BP measurement for accurate initial diagnosis, and the use of home and ambulatory BP monitors is encouraged to ensure strict 24-h (morning and evening) BP control. Lifestyle modifications are encouraged, especially in the elderly who are more responsive to salt restriction. Asian characteristics of HTN warrant further study. Enhanced salt sensitivity, high dietary salt intake, aging population, and obesity are just some of the different characteristics of Asian HTN. More importantly, stroke is a more common consequence of uncontrolled HTN in Asia (compared to coronary artery disease), with hemorrhagic stroke having a relatively higher prevalence. Hence, lower BP targets are needed since BP levels correlate more linearly with stroke. China, Japan, Taiwan, and Korea have come up with published guidelines, highlighting some key points and difference with the US and European guidelines. The Philippine Society of HTN also previously came out with the "140/90 Report," locally attuning foreign guidelines. Several years back, there has been a call for the development of our own Asian HTN guidelines. With newer findings on the benefits of lower BP targets/goals and its possible benefits to the Asian population and more findings on the different Asian characteristics of HTN, it might be the best time now to heed that call.

Key words: American college of cardiology/american heart association hypertension guidelines, asian hypertension guidelines, european society of cardiology/european society of hypertension guidelines, philippine society of hypertension

Introduction

Hypertension (HTN) remains to be the single most important risk factor for the development of cardiovascular (CV) disease, leading to premature death worldwide. It is said to be the most common, readily identifiable, and reversible risk factor for myocardial infarction, stroke, heart failure, atrial fibrillation, aortic dissection, and peripheral arterial disease, as well as chronic kidney disease and cognitive decline. The global burden of HTN is projected to rise even more in the

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coming years due in part to the obesity epidemic and the aging population. Moreover, yet, despite its high prevalence and its associated deleterious effects on various organ systems of the body, treatment remains inadequate in majority of patients, and control rates remain low.[1,2]

One area of concern with regard to HTN treatment is the control rate. Despite the availability of effective antihypertensive medications, and despite more aggressive campaigns to detect and treat HTN, control rates still remain low.[3] Back in 2009, the term "HTN paradox" was used to describe the situation, wherein there is more uncontrolled disease despite improved therapy. It is paradoxical that despite the various therapeutic advances proven in clinical trials, the number of people with uncontrolled HTN has continued to rise. In part, a critical factor in this increase is the failure to adopt healthy lifestyles, which must be addressed more urgently. Other possible reasons for the low control rates might be poor management of elevated systolic blood pressure (BP).[4] This might be due to poor compliance/adherence to medications and lifestyle modifications. Some authors blame physician inertia (or therapeutic inertia) as a cause of poor management of elevated BP.[5-7]

The Joint National Committee (JNC) on Detection, Evaluation, and Treatment of High BP published its first report back in 1976.[8] It was intended to give recommendations to help physicians who care for hypertensive patients achieve better results in prevention and management of HTN. Since then, these guidelines have been widely used by primary care physicians, who are the ones who handle the majority of hypertensive patients, and it has greatly improved the management of HTN since its introduction. Aside from JNC, the other two most commonly used guidelines are from the European Society of Cardiology and the National Institute for Health and Clinical Excellence (NICE) guidelines from the United Kingdom.

HTN guidelines such as the JNC provide recommendations for the prevention, detection, evaluation, and treatment of HTN, which aims to provide the greatest benefit to patients with the least amount of harm. It usually includes the best evidence available at that time. In 2014, the JNC passed on the responsibility of making HTN guidelines to the American College of Cardiology/American Heart Association (ACC/AHA), and 3 years later, in 2017, the ACC/AHA came up with a new set of guidelines which effectively "redefined" HTN. It was totally different from previous guidelines due to the lower threshold and targets. The following year, in 2018, the European Society of Cardiology/European Society of HTN (ESC/ESH) followed suit and came up with a much-awaited update to their own guidelines.

The recent change in HTN guidelines by the ACC/AHA in 2017, with its redefinition of HTN to a lower BP level of 130/80, has generated a lot of buzz in the medical world. In an article written by Poulter *et al*., for the International Society of HTN, they stated that these guidelines have many laudable recommendations but some, particularly the redefinition of the HTN threshold, are somewhat controversial.[9] Indeed, the new BP classification with lowered BP thresholds and targets promptly attained great attention and controversy worldwide.[10]

By coming up with a new diagnostic threshold and new therapeutic targets, it effectively introduced the concept of early treatment. Early detection of elevated BP and early management through non-pharmacologic/lifestyle modifications, pharmacologic treatment, or both can possibly delay the progression of HTN and in the long run promote CV protection and also minimize target organ damage. It was considered a shocking change because some of the evidence used were based on epidemiological evidence. On a positive note, the new guidelines emphasized the use of appropriate technique for BP measurement, which was discussed at length. Using the proper blood pressure equipment (especially correct sized BP cuffs) and using the proper technique for measurement (patient rested and seated quietly, feet flat on the floor, BP cuff at same level with the heart) invariably leads to an accurate diagnosis of hypertension. The guidelines strongly recommended the use of out-of-office BP measurements such as 24-h ambulatory BP monitoring (24-h ABPM) and home BP monitoring (HBPM). These are best used for white coat HTN, masked HTN, and nocturnal measurements to check for dipping. The use of CV risk stratification was reintroduced, which will help in deciding whether to use antihypertensive medications or not, especially in those with Stage I HTN, based on the patient's 10-year CV risk profile. Screening for secondary HTN was also recommended.[11]

Evidence to support the lower BP threshold of 130/80 mmHg came from two recent publications, the Systolic BP Intervention Trial (SPRINT) and the 2016 Lancet meta-analysis of randomized controlled trials (RCTs) of antihypertensive medications. The Lancet meta-analysis showed benefit in prevention of CV events with a BP reduction of 25%, while SPRINT, through the use of unattended automated office BP monitoring, yielded BP values 10–15 mmHg lower than routine clinic BP. Hence, the achievement of a systolic BP of 120 mmHg is postulated to be equivalent to 130–135 mmHg by routine clinic measurement. Recognizing the difference in the manner of BP measurement techniques, a BP value of 130/80 mmHg was deemed reasonable for use as both BP threshold and BP target. The core concept of earlier and tighter BP control is deemed to provide more sustained target organ protection and CV disease prevention. Strict BP lowering early in life is said to maintain vascular health, which is important later on in life as the patient ages. Focus was shifted to a practical approach through the use of HBPM which can help in determining efficacy of drug management when measured at trough levels early in the morning. Checking the BP in the clinic, at home, and the occasional use of ABPM will also help improve detection and management of white coat and masked HTN.[12]

The central controversy in the 2017 ACC/AHA Guidelines revolves around the new lower levels of 130/80 mmHg, thereby increasing the prevalence of HTN and diagnosing more hypertensive subjects <65 years old. Along with this concern was the increased number of patients getting medication. However, as explained by the authors, therapy will only need

to be initiated in only a small percentage more, because at the lower BP levels in Stage I, pharmacological treatment only needs to be initiated for those with high CV risk. This will not significantly affect cost-effectiveness ratio. From the clinical point of view, patients who are detected early will benefit with closer and earlier follow-up, and in the future, earlier initiation of antihypertensive medications will prevent HTN-mediated organ damage (HMOD).[13]

Probably as a result of the controversy, the 2017 ACC/ AHA Guidelines effectively increased the awareness with regard to importance of elevated BP as a cause for CV morbidity and mortality throughout the world.[9] Suddenly, people all over the world started talking about their BP levels and their CV risk profile. It effectively forced people to take charge and be in control of their BP. One author puts it quite nicely: Changing the cutoff values for HTN diagnosis might be an important way to force patients to follow-up with their doctors, and persuade them to change their lifestyle and use non-pharmacologic methods to reduce BP and thereby prevent, protect from, or delay onset of HMOD.[13] However, caution should also be exercised because inappropriately labeling people as hypertensives might cause undue anxiety, or there might be unnecessary antihypertension medications that will be given to younger people who are low risk.[9]

Last September 2018, the ESC/ESH came out with an update to their own HTN guidelines. In general, the European guidelines are more conservative, using the same traditional BP categories from their previous guideline, thereby using a higher threshold for Stage 1 HTN defined as office BP values of 140–159/90–99 mmHg compared to the 2017 US guidelines. This is actually based on evidence from multiple RCTs showing clearer benefit with higher thresholds. Like the US guidelines, it also recommends lifestyle interventions, as well as regular use of HBPM, with ABPM as an option.[14] Based on the guidelines, it is recommended that treatment be initiated with a two-drug single-pill combination treatment, except in the low-risk, the frail, and very old hypertensive patient. This is meant to enhance compliance and control rates. Likewise, simple algorithms replaced complicated guidelines for primary care physicians who see majority of patients. Traditional BP categories were maintained, primarily due to clearer benefits from RCTs using these thresholds. Finally, in contrast to the American guidelines, the European guidelines are not as aggressive in lowering target BP to reflect SPRINT data.[15]

Recognizing the difference in recommendations and the level of evidence used in these guidelines, the concern was shifted to implementation of these same guidelines at the last year's Annual AHA Convention. Taking into account differences in genetics, race, diet, etc., the more important question now is if these guidelines could apply to other populations.[16] Some Asian countries, namely China, Japan, Korea, and Taiwan, recognizing differences in genetic makeup, lifestyle, diet, etc., adapted some of the recommendations from the previous US and European guidelines and tried to modify it to suit the needs of their specific countries.

In a commentary in the International Journal of Preventive Medicine AK Gupta said that, with the exception of the NICE guidelines, none of the existing HTN guidelines at that time took into account phenotypical characteristics such as race, age, obesity, and plasma renin activity. Racial differences, leading to differing responses to different classes of antihypertensives, include those who are of African American descent, who have higher salt sensitivity and low plasma renin activity, and South Asians with a higher prevalence of central obesity and insulin resistance, with HTN driven mainly by high sympathetic activity. African Americans respond better to CCBs and diuretics, while Asians fare better with angiotension-converting enzyme inhibitors.[17]

Ernesto Schiffrin, MD, from McGill University in Montreal, emphasized that ethnicity may affect an individual's response to treatment, and instead of universal application, stressed that guidelines should be adapted to the local setting.Likewise, George Bakris, MD, from University of Chicago Medicine, stated that culture and location must be considered in the interpretation of clinical trial data, so it is not a one-size-fits-all proposition. This is the reason why Japan requires that studies in Japanese people should be done before guidelines are accepted.

In 2015, Jeong Bae Park, MD, from Cheil General Hospital/ Dankook University College of Medicine, stated the need for Asian guidelines on HTN, enumerating various characteristics of Asians and Asian HTN, namely rapid aging of their societies, a high prevalence of metabolic diseases constituting a "metabolic pandemic," due in part to adoption of Western lifestyles, high salt intake in diets despite various efforts by their own governments, and a relatively high risk of stroke compared to coronary artery disease, with a stronger relationship between BP level and stroke (compared to Westerners).[18]

Back in 1979, Dr. Ramon F. Abarquez, Jr., founder of the Philippine Society of HTN (PSH), was the first one who pushed for the treatment of HTN starting at a level of 140/90 mmHg, which was then still considered by international experts as normal BP. At a time, when HTN was still defined as a BP of 160/100 or higher, Dr. Abarquez and his team at the University of the Philippines-Philippine General Hospital presented a paper showing that at a level as low as 140/90 mmHg, there were already abnormal changes in the heart and arteries of the individual.[19]

To date, the following countries have published their own guidelines on hypertension: China (2011), Korea (2013), Japan (2014) and Taiwan (2015, with focused update in 2017). The Philippine Society of Hypertension launched their own guidelines in 2012, called the Philippine Clinical Practice Guidelines (CPG) on the Detection and Management of Hypertension (also called "140/90 Report: MultiSectoral Task Force Consensus on Hypertension"), which is due for update anytime soon.[20]

In a series of articles published in Pulse (Basel) in 2015, presenting the Chinese, Korean and Japanese Guidelines, the authors stated that the identification of similar characteristics of hypertension in Asians will hopefully lead to future discussions

on a possible common hypertension guidelines for Asia. At that time, there was increased prevalence of hypertension in China but awareness and control rate remain unchanged. Such an increase was brought about by an increase in the elderly population, and also abrupt changes in lifestyle like high salt, sugar, fat and calories in the diet, plus low physical activity and increased anxiety and stress in work.[21] The Korean guidelines identified sodium reduction as the most important lifestyle change needed to help curb HTN. The risks for cerebrovascular disease and coronary artery disease (CAD) were highest in Korea. Their guidelines classified pre-HTN further into Stage 1 and Stage 2 prehypertension based on office BP because they have shown that CV risks are significantly different in both stages.[22] The Japanese had the highest intake of salt in the diet, coupled with genetically high salt sensitivity. They also recognized the higher prevalence of stroke in Asian hypertensives (vs. CAD in Caucasians), and the steeper association between level of BP and stroke, such that they emphasized the importance of strict 24-h BP control, taking into account both the morning BP surge and nocturnal BP increase. They were one of the first to advocate the use of HBPM in the Ohasama study. Likewise, it was recommended that obesity and related metabolic syndrome should be addressed by lifestyle modifications.[23] The Taiwanese guidelines recommend the use of both traditional office BP measurements and unattended automated office BP measurements (AOBPM) and, in 2017, revised their BP treatment targets to more intensive levels. Using intensive BP strategies will benefit a large group of hypertensive patients and with aggressive BP targets foresee that CV events in Taiwan will substantially decrease. The use of AOBPM is recommended for intensive BP targets, with HBPM as surrogate.[24]

Differing characteristics of Asian HTN underscore the need for HTN guidelines developed specifically for the Asian population. The rapidly aging population, prevalence of obesity and metabolic syndrome as a consequence of adoption of Western lifestyle, high salt intake, and the different stroke/ CAD profile represent major differences compared to Western hypertensives.[18] Stroke, especially hemorrhagic stroke, and non-ischemic heart failure are commonly seen in Asia as a result of HTN, with a stronger association between BP levels and stroke. This might be related to early morning BP surge and to high sodium intake. Higher salt sensitivity due to salt-sensitive gene polymorphism of the renin-angiotensin system also plays a role. Strict 24-h BP control is, therefore, important in Asia, and a practical step for strict control on an individual level is HBPM. To better understand the management of HTN in Asians, more clinical studies should be done to investigate Asian characteristics of HTN.[25]

In summary, the recent change in diagnostic threshold and treatment targets of the US guidelines might benefit the Asian hypertensive more than the European guidelines. Considering that stroke is the more common sequelae of HTN in Asians, a lower target will definitely benefit them more since stroke and BP exhibit a linear relationship. Strict BP control for the whole 24-h will also be beneficial, and this can be achieved by checking home BP, as recommended by both the US and European guidelines. The early morning BP surge as well as nocturnal HTN will be detected early and appropriate treatments given early, too. Salt plays a major role in causing HTN in Asians, who have high salt intake in the diet aside from higher salt sensitivity. In this regard, elderly patients have been shown to respond well with salt restriction, although younger hypertensives and even those without HTN will benefit from salt restriction. People who are diagnosed to have Stage 1 HTN will benefit from lifestyle modifications, and with regular follow-up, the transition to higher levels of BP will be detected early; hence, medications can be started early depending on the CV risk of the individual. However, cost-effectiveness of such a strategy is subject to debate. Increased awareness is the key to earlier detection, prevention, and management.

Several years back, there has been a call for the development of Asian HTN guidelines, considering the differences in clinical phenotypes of HTN, and response to treatment. Now might be the best time to heed that call.

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Review Article

Advocating Home Blood Pressure Monitoring in Improving Hypertension Control in the Philippines

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Abstract

Obtaining a target goal blood pressure (BP) is crucial in the management of hypertension so as to prevent cardiovascular disease, kidney failure, and stroke. Home BP monitoring is one method to achieve target pressure and has the potential to improve the outcomes of hypertensive patients. Several advantages have been identified with the use of home monitoring, particularly in properly diagnosing white coat and masked hypertension. Studies have shown that home monitoring significantly reduce BPs, may improve compliance and lessen therapeutic inertia. It has a significant correlation with cardiovascular risk factors and appropriate control may reduce mortality. The downside in the use of home monitoring is the cost of validated automatic machines, which may be expensive for Filipino patients. Despite that limitation, home monitoring of BP may be incorporated into the care for Filipino patients with hypertension.

Key words: Ambulatory blood pressure monitoring, home blood pressure monitoring, hypertension, office blood pressure monitoring

Introduction

High blood pressure (BP) is the most common modifiable cardiovascular risk factor worldwide. Guidelines have been formulated all over the world addressing the issue of hypertension; however, the control rates for hypertension remains discouraging, particularly in the Philippines. In the latest National Nutrition and Health Survey, the prevalence of hypertension in the Philippines is 22.3% and is highest in individuals more than 70 years old. The problem with the survey that measurement was based only on single measurements done in doctors' clinics.[1] The use of conventional measurement of BP done in the office BP monitoring (OBPM) has been the norm in the diagnosis and management, but this method has downsides, particularly of white coat hypertension and masked hypertension, which are quite common for both untreated and treated hypertensives. The reliability of OBPM is questioned with issues such as the unstandardized setting and conditions of clinics, observer bias and errors, and the small number of readings. There is also a discordance in the measurements of OBPM compared to out-of-office BP (OBP) measurements which could have an effect on the "true underlying BP reading" of the individual.[2]

Home BP monitoring (HBPM) refers to the measurement of BP at home, ideally by the individual. It is optimal when the patient is seated at rest at around the same time in the morning and evening, usually a period of 1 week.[2,3] The readings are recorded using a validated, automated BP device and are then conveyed to the physician for interpretation. This method is appealing to most patients and can lead to more awareness and control of their hypertension. HBPM allows standardization of conditions, leading to little measurement variability and reproducibility of readings. Home BP (HBP) measurements can easily identify patients with white coat, masked, and sustained hypertension. HBPM is also widely available and can provide day-to-day BP variability values.[3-5] Despite the several advantages of HBP measurements, it has yet to gain popularity in the Philippines due to the cost of the automated BP machines, lack of patient training, and the preferential use of OBP of physicians.

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HBP and its Impact in Cardiovascular Disease

Out-of-OBP readings taken multiple times have a better predictive value than OBPM regarding BP-related outcomes. Compared with clinic BP, HBPM has stronger associations with target organ disease. A meta-analysis examined the association of HBPM versus OBPM and ABPM, and analysis of the 10 studies included showed that HBPM has a stronger correlation with echocardiographic left ventricular mass index compared to OBPM.[6] Another meta-analysis demonstrated that HBPM is a stronger determinant of proteinuria than OBPM.[7]

The ultimate objective for a diagnostic method to assess a cardiovascular risk factor is its ability to predict future cardiovascular events. In prospective studies included in a meta-analysis of about 17,000 patients, HBPM showed to be superior to OBPM and is a significant predictor of cardiovascular mortality.[8] In the international database of HBP in relation to cardiovascular outcome study, participants with optimal or normal OBPM, hazard ratios for a composite cardiovascular endpoint associated with a 10 mmHg higher systolic HBPM were 1.28 and 1.22, respectively. At high-normal OBPM and in mild hypertension, the hazard ratios were at about 1.20 for all cardiovascular events and 1.30 for stroke. HBPM has an independent prognostic value for cardiovascular morbidity and allows for a more accurate risk stratification than OBPM.[9]

HBPM for Detection of White Coat and Masked Hypertension

The use of the 24 h ambulatory BP monitoring (24 h ABPM) is considered the gold standard in determining white coat or masked hypertension. White coat hypertension is defined in the latest report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines[10] as higher OBP measurements than out-of-OBP readings and is considered significant if BP readings are >20/10 mmHg higher than HBPM or 24-h ABPM. Masked hypertension, on the other hand, is defined as controlled OBP readings but uncontrolled out-of-OBP settings. The risk for cardiovascular disease and all-cause mortality with masked hypertension is similar to that with sustained hypertension and about twice as high in the abovementioned risk with normotensive patients. The inaccessibility of a 24-h ABPM in most clinics in the Philippines makes HBPM the ideal method in detecting white coat and masked hypertension. Both methods employ multiple measurements in the usual environment of each individual; however, there are a few differences. HBPM is performed while the patient is seated and has rested for a few minutes, while the ABPM is performed in fully ambulatory conditions and postures at home, work, or during sleep. However, despite these differences, average HBPM and daytime ABPM appear to have similar thresholds and diagnostic accuracy for white coat and masked hypertension.[10]

HBPM and its Impact in BP Control

Patients who are monitoring their BP at home have been shown to improve control, with the use of HBPM associated with significant reductions in systolic and diastolic BP and reductions in antihypertensive medications compared to usual care.[11] Advocating HBPM in hypertensive patients has reduced therapeutic inertia, which is defined as unchanged medications despite the elevation of BP. However, simple home monitoring is not enough in BP control of patients. There should be interaction between the patient and their doctor. Telemonitoring has been utilized when doing HBPM, whereby the BP readings are instantly relayed to a primary health-care professional who can guide treatment along a predetermined algorithm. The use of telemonitoring avoids travel for the patient and saves time for the health-care team. There are some small studies suggesting that the use of HBPM may improve adherence of patients to their medications, but guidelines, such as the UK NICE guidelines, still recommend a 24-h ABPM.[11]

Cost-effectiveness of HBPM

The only issue in the use of HBPM in the Philippines is the cost of the validated automatic BP machines. There is no health economic assessment using HBPM in the country. There is a strong call to create such studies, particularly in an out-of-pocket economy like ours. There are data in other countries, where HBPM has been shown to be cost neutral after taking into account the number of consultations, drugs, referrals, equipment, and training expenses.[12] However, it is cost effective in terms of reduced medication and insurance savings, particularly in patients identified with white coat hypertension. A meta-analysis showed that HBPM may be associated with lower medical cost but may be offset by equipment and technology costs related to telemonitoring.[2] Telemonitoring is not available in the Philippines.

Procedures for Using HBPM

The latest American College of Cardiology/American Heart Association (ACC/AHA) guidelines for hypertension have outlined the steps in conducting BP readings at home. It is recommended that the individual should be trained by their physicians regarding information about hypertension and how to select the appropriate equipment to use. The patient should also realize that there might be variability in individual results. The physician must also educate the patient to interpret the results.[10]

The automated device should be verified and validated. The use of auscultatory devices is not recommended as the patients may not master the technique necessary for measuring of BP. The appropriate cuff size must fit in the arm, and interarm differences are significant. If the differences are significant, the arm with the higher readings should be used.[10]

During the procedure, the patient must remain still and avoid smoking, exercising, or drinking coffee within 30 min before BP

measurements. The patient must be able to rest at least 5 min before doing the measurements. The patient should sit correctly, with his back straight and supported, feet flat on the floor and uncrossed, and the arm supported on a flat surface. Ideally, multiple BP readings, at least two readings 1 min apart before taking medications and in evening before supper, should be taken. The BP should be recorded accurately and be obtained at least 2 weeks after a change in the treatment regimen and during the week before a clinic visit.[10]

Conclusion

OBP measurements are necessary in diagnosing hypertension, but HBPM may be a necessary adjunct in establishing and monitoring BP trends and differentiating white coat and masked hypertension. We advocate the use of HBPM in Filipino hypertensive patients but should take consideration the cost of the validated machines.

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Review Article

Revisiting Salt Sensitivity and the Therapeutic Benefits of Salt Restriction in Hypertension

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Abstract

The effects of excessive dietary salt on blood pressure (BP) vary in certain individuals, with some developing a hypertensive response to salt loading (salt-sensitive individuals), while some do not experience any increase in BP (salt-resistant individuals). There are mechanisms that enable an individual to adapt to a high-salt load, and hypertension develops only when the kidney's ability to excrete excess salt is impaired. At present, there are no clinically practical tests available to determine salt sensitivity, and more research is needed so that in the future, a drug specifically working on salt sensitivity will be developed. The effects of high salt diet on gut bacteria and its relationship with diet and disease is an exciting new area of research. Nonpharmacologic and lifestyle modifications, delving on weight loss, exercise (that promotes physical fitness), diet (especially Dietary Approaches to Stop Hypertension diet), and other nutrients (such as potassium and flavonoids) should be emphasized to both hypertensive as well as non-hypertensive patients. The next generation should be taught to not only limit their salt intake but also they should learn to eat healthy to prevent chronic diseases later in life. Clinicians should, therefore, play a more active role in promoting lifestyle changes, most especially dietary salt restriction, and empower patients to take charge of their health, keeping in mind that the strongest benefit can be attained by doing lifestyle interventions in its totality.

Key words: Gut microbiome in salt-sensitive hypertension, non-pharmacologic and lifestyle interventions, salt in hypertension, salt sensitivity, therapeutic lifestyle changes

Introduction

Hypertension is a major health problem with a high prevalence, putting the patient at risk for cardiovascular disease. Many factors contribute to the high prevalence rate of hypertension, namely poor diet, excess body weight (overweight and obese), alcohol abuse, physical inactivity, aging, stress, plus socioeconomic determinants, and inadequate access to health. Among these, dietary salt intake remains to be one of the most important contributing factors to the development of hypertension.[1]

Salt and Sodium

Salt plays a major role in the civilized world. It is mainly used as food flavoring, in addition to spices, and also as food preservative. It is also used as antiseptic. There was a time when it was even used as a form of currency for trading.[2]

In the United States, it is usually referred to as sodium, while in most scientific literature, it is commonly referred to as salt (sodium chloride). Salt contains 40% sodium and 60% chloride. Sodium is an important mineral because it is involved in many

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essential processes in the body. It is needed for nerve impulse conduction, muscle contraction, and relaxation, as well as water and electrolyte balance.[3]

Sodium is found naturally in certain foods such as eggs and vegetables. Among the sources of salt in the diet, the highest contribution is from packaged and processed foods, comprising about 75–80%, including restaurant foods. Only 10–12% is naturally-occurring, 5% comes from added salt during cooking, and another 5% added as condiment at the table.[4]

Despite efforts to educate patients on the ill effects of excessive salt in the diet, especially in hypertensive individuals, clinicians still face a very challenging task due to the ubiquitous nature of salt. It is essential that patients get a clear understanding of what salt/sodium is and what is the salt content of various food sources.

Salt and Hypertension

The human body only needs an estimated 500 mg of sodium to perform its vital functions. Yet, most people consume a lot more than what is needed.[3] With a high-salt diet, there will be consequent water retention, and this will entail an increase in the blood pressure (BP) to excrete the excess salt.

In the normal individual, a sequence of events leads to the return of arterial pressure to near normal levels as follows: An increase in salt intake will produce an increase in extracellular fluid volume, which, in turn, will increase arterial pressure. This increase in BP will increase blood supply to the kidneys, thereby reducing renin and angiotensin, leading to a decrease in renal retention of water and salt, and a return of extracellular volume to near normal levels. This eventually leads to a decrease of BP to almost normal levels.[5]

With any increase in arterial pressure, there is a consequent pressure natriuresis which aims to increase excretion of sodium and water through the kidneys. Hypertension develops only when the kidney's ability to excrete sodium becomes impaired.[6]

Salt-sensitive and Salt-resistant BP

As stated previously, sodium is important because it is involved in certain processes in the human body, performing essential cellular functions, regulation of fluids and electrolytes, with consequent maintenance of an optimal BP. However, the question remains, why do some individuals develop a hypertensive response to a high-salt diet, while some do not. The body's natural response is to excrete dietary salt through an increase in BP, or what is called pressure natriuresis, but some individuals are able to do so without needing an increase in arterial BP. Individuals who develop an increase in BP with a high-salt load are said to be "salt sensitive," while those who do not are "salt resistant." The underlying mechanism is complex, involving both genetic and environmental influences.[6]

It has been estimated that in hypertensive individuals, 50% are salt sensitive. On the other hand, 25% of normotensives are also noted to be salt sensitive. If no intervention is done, such as lifestyle and dietary changes, there is a chance that these normotensive individuals who are salt sensitive will become hypertensive in the future. Other ill effects of a high-salt diet include stomach cancer, kidney disease, and an adverse effect on metabolism causing obesity.[7]

The clinical significance of the salt-sensitive phenotype is that it serves as a strong cardiovascular risk factor for cardiovascular morbidity and mortality, independent of chronic hypertension. Prognostic implications are said to be as strong as other traditional risk factors. In this regard, more research should be done, especially on drugs that act directly on the causes of salt sensitivity itself and not on hypertension only. As of now, there are no practical tests that can be used clinically. The present laboratory techniques are too costly and hard to do, making it impractical for clinical use.[8]

The Gut Microbiome and Probiotics

An intriguing concept that is still in the experimental stage is the role of the gut microbiome in patients who develop hypertension in relation to a high-salt diet. If validated, it could probably lead to newer treatments directed at salt sensitivity itself.

In animal studies, foods with high-salt content have been shown to have an adverse effect on gut health, causing tissue inflammation and autoimmune disease.[9] One study has shown that a high-salt diet causes depletion of *Lactobacillus murinus*, such that subsequent treatment with the same prevented aggravation of salt-induced hypertension.[10]

Aside from depletion of *L. murinus*, too much salt can also stimulate inflammation, leading to hypertension in the long run. The researchers from the Massachusetts Institute of Technology showed that probiotics can potentially reverse the effects of too much salt in the diet. The exact mechanisms are still unclear, and more research should be done in the future to learn about the relationship between gut bacteria, diet, and disease.[11]

Dietary Salt Restriction and its Effects on Hypertension

Dietary sodium has been associated with an elevation in BP in various clinical, epidemiological, and experimental studies. Hence, it was considered good advice to reduce salt intake in the diet through various means, and in this regard, patient education plays a major role. A reduction in salt intake has been shown to lower BP, more so in the elderly, in obese individuals, and in African Americans.[12]

Since our dietary/eating patterns are considered as learned behavior, there is a possibility that the taste for salty diets can revert back to a lower salt diet. It has been shown that as people are slowly given a lower salt diet, the preference for salty foods also changes. However, consumers find it hard to avoid dietary salt mainly due to the preponderance of salt in packaged and processed foods. Restaurant food is also known to contain high

levels of salt to make the food more palatable to majority of consumers.[13]

In addition to sodium's direct BP effects, the benefits of dietary salt restriction extend to improvement in response to certain antihypertensive medications. A low sodium diet will improve BP-lowering effects of most hypertension medications with the exception of calcium channel blockers. It can also decrease potassium loss associated with the use of diuretics. More importantly, it has been shown that there is a better response to angiotensin-converting enzyme inhibitors or angiotensin receptor blockers if patients stick to a low-salt diet.[14,15]

Non-pharmacologic Therapy of Hypertension with Focus on Salt Restriction

Almost all hypertension guidelines recommend dietary salt restriction, but the levels may vary: the World Health Organization (2013) recommends <2000 mg/day of sodium, while the United States Department of Agriculture (2015) recommends ≤2300 mg/day of sodium, and the American Heart Association set their recommendation at an upper limit of 1500 mg/day of sodium.

Salt reduction in the diet entails a change in behavioral pattern as well. In certain cases, it might be helpful to employ the services of a dietitian for reinforcement. The internet is replete with good and bad advice, and it would be better if they are counseled on how to seek accurate and reliable information.

Most guidelines emphasize the need for non-pharmacologic therapy and lifestyle modifications in addition to pharmacologic therapy for hypertension. Therefore, clinicians should play an active role in promoting lifestyle changes, most especially dietary salt restriction. Patients should be made aware that significant BP reductions can be realized with more stringent lifestyle modifications, empowering them to take charge of their health.

There is a linear relationship between weight loss and BP; hence, it should be maintained through proper diet and exercise. If weight is regained, the BP benefit will be lost. Exercise, or any physical activity, should promote physical fitness, which is the physiological benefit that patients get from exercise. However, it should be stressed that only modest exercise is needed to realize benefit for BP reduction since physical activity reaches a plateau beyond which there is no more benefit for the BP. Hence, heavy and strenuous exercise is not actually recommended for BP control. On a positive note, a desirable side effect of exercise is weight loss.[12]

With regard to diet, majority still recommend the Dietary Approaches to Stop Hypertension (DASH) diet. The DASH diet (rich in fruits and vegetables, with the use of low-fat dairy products, and low in saturated fats) is independently effective in reducing BP. Likewise, the addition of mineral nutrients, especially an increase in potassium intake, has been shown to help in reducing cardiovascular risk. Flavonoids from cocoa and berries have been shown to have a modest effect on BP.[12]

Summary

Excessive salt intake has been shown to increase BP eventually leading to sustained hypertension. There are mechanisms that enable an individual to adapt and respond to a high-salt diet, but those who are salt sensitive will eventually develop hypertension if left untreated. Even in persons who are not hypertensive, the recommendations to lower salt intake still apply. In theory, sodium reduction by producing lowering of BP can reduce cardiovascular disease. The new concept exploring the relationship between gut bacteria, diet, and disease is promising.

It is imperative that the future generations should be taught not only to limit their salt intake but also, more so, they should learn to eat healthy to avoid developing chronic conditions such as hypertension, diabetes, and obesity. Most guidelines emphasize the need for more stringent lifestyle modifications in all stages of hypertension. Clinicians should, therefore, play a more active role in promoting lifestyle changes, most especially dietary salt restriction, and empower patients to take charge of their health, keeping in mind that the strongest benefit can be attained by doing lifestyle interventions in its totality.

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Original Article

The Effectiveness of a Training Program for Advanced Practice Nurses in the Philippines on the Care of Patients with Primary Hypertension

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Abstract

Background: The same problems of access to health care due to inadequate and inequitable distribution of human resources for health continue to be present in countries worldwide, including the Philippines. However, these conditions have not stimulated the development of the role on advanced practice nursing (APN) in the country, despite hypertension (HTN) being a prevalent public health problem that can be addressed at the primary care level. Nurses, being the most numerous health professionals, can be trained to fulfill this deficiency. **Objective:** This study aimed to determine the validity and effectiveness of the investigator-designed HTN training program for advanced practice nurses. **Methods and Design:** This was one group, pre-test-post-test design, involving nursing clinics for wellness in a government-subsidized university, located in Manila, the Philippines. Out of the 28 masters-prepared nurses who consented, 24 participants completed the training program and answered the post-training instruments; the majority were females, with a mean age of 32.42 years (standard deviations [SD] = 8.397) and mean the clinical experience of 5.84 years (SD = 3.503). A panel of six experts reviewed and validated the seven modules for the HTN training program. It consisted of lectures, demonstration sessions, small group discussions, oral examination, skill performance evaluation, and clinic visit with a demonstration, totaling 32 h of in-person training. Participants took the written examinations before and after the training program. **Results:** The expert panel determined that the module content covered the learning objectives adequately. After the training program, the total knowledge score of the participants increased from 33.00 points (SD = 5.25) to 43.08 points (SD = 43.08), which was statistically significant ($t = -11.245$, $P < 0.001$). Furthermore, self-efficacy scores increased significantly ($t = -6.187$, $P < 0.001$), from 8.08 points (SD = 1.16) to 9.06 (SD = 0.69). **Conclusions:** The validated HTN training program module effectively equipped the masters-prepared nurses with the required knowledge, skills, and attitudes in providing entry-level APN care for patients with primary HTN, addressing the competencies outlined by the National Organization of Nurse Practitioner Faculty in the United States. Since the positive outcomes on the nurse participants translated to the patient outcomes seen in the advanced practice nurse-led HTN Clinic done after this study, the competencies included in the training program modules should be integrated into the country's master's degree curriculum in Adult Health Nursing to provide adequate preparation for entry-level APN care.

Keywords: Adult Health Nursing, advanced practice nursing, hypertension in the Philippines, nursing education research

Introduction

Hypertension (HTN) is a significant public health issue affecting billions of people around the world[1] and the leading risk factor for global mortality and morbidity.[2] More than half or 55% of the 17 million deaths from cardiovascular diseases (CVDs) annually are attributed to HTN. In the Philippines, 33% of the proportional mortality accounted for noncommunicable diseases is due to CVDs, which include

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HTN.[1] The PRESYON 3 study found a 28% prevalence of HTN among Filipinos aged ≥18 years, representing a 150% increase from 11% in 1992 to 28% in 2013 and most prevalent among adults aged 70 years and higher only 57% of people on blood pressure (BP).[3]

Chronic diseases such as HTN are best addressed at the primary care level to ensure continuity of care. With the inadequate and inequitable distribution of human resources for health, health care for patients with chronic diseases such as HTN becomes too fragmented and the continuity elusive due to the shrinking number of primary care physicians.[4] In the Philippines, nurses, being the most numerous health-care professionals in the country, can be trained as advanced practice nursing (APN) practitioners to help manage HTN in community primary care settings.[5] This study aimed to determine the validity and effectiveness of the investigator-developed HTN training program for APNs.

Materials and Methods

Study Design

A one-group pre-test post-test design was used to evaluate the effectiveness of the training program comparing the knowledge and self-efficacy of the APNs before and after the additional training in the management of patients with primary HTN. This pre-experimental design, often used in evaluating educational interventions, was chosen to explore if the training program is feasible and can be used in further investigations.

Study Setting

This study took place in the City of Manila, the Philippines, a highly urbanized city with high population density and reported prevalence of HTN at 21.7%.[6] Specifically, the nursing clinics for wellness of a government-subsidized university, located in District V in the City of Manila, was the setting of recruitment and conduct of the training program.

Study Participants

The sample size needed for a paired *t*-test, given a moderate effect size of 0.6, an alpha of 0.05, a power of 0.80, was 24 nurses. The sample size and statistical power were computed using the G*Power software (version 3.1.9.2).

Institutions in the City of Manila that offered master's degrees in nursing, with a major in Adult Health Nursing provided a list of prospective participants with their latest contact information. Eligible nurses received letters of invitation by electronic mail, followed with text messages and phone calls as needed. Other recruitment strategies used were done through referrals, and posting of recruitment materials online and in bulletin boards of hospitals and the headquarters of the Philippine Nurses Association in Malate, Manila.

Inclusion criteria were: (1) Graduate of an accredited master's program in nursing, with a major in Adult Health Nursing, or at least have completed all major and core courses, (2) valid license to practice, (3) minimum of 2 years of hospital experience, preferably in an ICU setting, (4) willingness to undergo a 32-h training, and (5) willingness to conduct clinic consultation with patients who have primary HTN while collaborating with a physician, and (6) signing an informed consent form.

Exclusion criteria were: (1) Graduate of a master's program in nursing, with a major other than Adult Health Nursing track, such as Maternal and Child Nursing, Community Health Nursing, Psychiatric and Mental Health Nursing, nursing education, nursing administration, disaster management, etc., or (2) refusal to sign the informed consent.

A total of 28 nurses consented to undergo training and completed the pre-test. However, four nurses were unable to attend the training due to work schedule and other constraints. Twenty-four participants completed the training and answered the post-intervention instruments.

For the purpose of this study, these nurse participants were called Advanced Practice Nurses, consistent with the definition adopted by the International Council of Nurses (2008): A registered nurse who has acquired the expert knowledge base, complex decision-making skills, and clinical competencies for expanded practice, the characteristics of which are shaped by the context and/or country in which s/he is credentialed to practice. A master's degree is recommended for entry level.

Validation of The Training Modules

A panel of six experts reviewed and validated the modules used in the HTN training program. The panel ensured that the learning objectives and content adequately addressed the relevant competencies according to the US-based National Organization of Nurse Practitioner Faculties (NONPF) (2014). Six experts composed the panel: (1) A master's prepared primary care nurse practitioner (NP) in a large federal facility in Washington DC in the US with 16 years of experience managing patients with HTN, (2) a staff RN with 25 years of experience working in a medical-surgical ward of a large teaching hospital in Manila, the Philippines, (3) a nurse educator with more than 20 years of experience teaching cardiovascular nursing at the master's level in Manila, the Philippines, (4) a health professions education expert with 5 years' experience in module development, in Manila, the Philippines, and (5) two primary care physicians in general practice with a total of over 20 years' experience in managing patients with HTN.

The experts reviewed each module and rate whether each competency/learning objective is covered adequately in the module by checking the appropriate column in the 4-point Likert Scale: Four for adequate, three for moderately adequate, two for somewhat adequate, and one for not adequate. They also wrote their recommendations and remarks in a separate column.

Intervention

The seven modules in the HTN training program covered topics in Table 1, addressing the applicable competencies identified by the NONPF (2014). The training lasted for 4 days or 32 h.

After signing the informed consent, the APNs completed the baseline instruments regarding knowledge and self-efficacy on HTN management (n = 24). The training program accommodated the different schedules of the participants which included the following modes: Classroom-based training in the nursing clinics for wellness (n = 7), and individual or small group training sessions for those with challenging schedule (n = 17).

Two other experts facilitated the lectures, demonstration sessions, and small group discussions: A physician with a specialty in CVD discussed the pathophysiology of HTN and pharmacologic therapy. The principal investigator, a board-certified adult NP with over a decade of experience as an independent health-care provider in California, USA, handled the remaining topics.

The physician and the NP/principal investigator prepared an oral examination, focusing on a case study to demonstrate clinical decision-making (assessment, differential diagnosis, and treatment plan) as well as other competencies (practice inquiry, quality improvement, and motivational interviewing).

The skills performance evaluation was an objective, structured, clinical examination on the following: History taking and risk factor assessment, cardiovascular physical assessment, and patient teaching.

The clinic visit and demonstration session introduced the APNs to the collaborative role of managing patients with primary HTN. During the first 4 h, the NP/principal investigator discussed the process of conducting an initial patient consultation and a follow-up visit. Then, the NP/principal investigator conducted the sample patient consultation and demonstrated the application of the skills discussed during the previous sessions of the training program. The next 4 h were dedicated to the extensive practice of the skills learned during the didactic sessions. The participants did return demonstrations of the simulated clinic consultations. Each APN had an assigned partner to obtain the health history and conduct the physical assessment. The APN discussed his or her findings and treatment plan with the NP/principal investigator and a physician after which, the APN counseled the partner/patient on the pharmacologic and non-pharmacologic interventions that they would prescribe. The NP/principal investigator and the collaborating physician evaluated the consultation done by the APN trainees.

Research Instruments

The investigator-developed instrument that measured knowledge on HTN management was based on the content of the modules in the HTN training program. Test items in this tool were written based on the objectives and content of the training modules, Adult-Gerontology, and Family NP Certification Examination Review Questions and Strategies[7] and Family NP Certification Intensive Review Fast Facts and Practice Questions.[8] To ensure the validity of the tool in meeting the objectives of the learning modules, the items were clustered in a test blueprint according to the objectives and the classification of the question (recall, understand, analysis, apply, or synthesis). Another panel of experts reviewed the knowledge instrument to establish the scale's content validity. The panel included the following experts: (1) A board-certified gerontology NP with a PhD in Nursing, practicing in California, USA with an expertise in managing patients with HTN, (2) a registered nurse in Manila, the Philippines with 5 years of experience taking care of patients with high BP, (3) a nurse educator with 14 years of experience teaching cardiovascular nursing at the master's level,

Table 1: List of modules, schedules, and time allotment

Session	Topic	Time allotment
Day 1	Module 1: Pathophysiology of hypertension	1 h lecture/discussion
	Module 2: Clinical decision-making in hypertension – assessment	2 h lecture/discussion 2 h demonstration/validation
	Module 3: Clinical decision-making in hypertension – non-pharmacological treatment	2 h lecture/discussion 1 h demonstration
Day 2	Module 4: Clinical decision-making in hypertension – pharmacological treatment	2 h lecture/discussion 1 h small group discussion
	Module 5: Patient teaching – motivational interviewing, anticipatory guidance, and counseling	1 h lecture 1 h demonstration
	Module 6: Practice inquiry: Identifying clinical practice issues, appraising evidence	1 h lecture/discussion 30 min small group discussion
	Module 7: Quality improvement, patient safety, and collaboration	1 h lecture 30 min small group discussion
Day 3	Clinic visit and demonstration	4 h demonstration 4 h return-demonstration
Day 4	Written examination	2 h
	Oral examination	2 h
	Skill performance evaluation/validation	4 h

(4) an expert in health professions education with an experience in module development, and (5) two practicing physicians with expertise in managing patients with HTN, with 35 and 11 years of experience, respectively. They evaluated the questions in terms of being representative of the objectives of the training, relevant to the concept being measured, and clarity of wording. General recommendations for each item were also asked and classified as "retain," "revise," or "drop." The experts were provided a space wherein they can add their comments and remarks for each item.

Four items were judged unclear, and therefore, were revised for clarity. In addition, the expert panel recommended to drop five items from the initial pool of questions. These were judged as either too basic for APN or not relevant to the construct being measured. After replacing the dropped items, the panel reviewed the questionnaire again. The content validity index for the final scale was 0.9815. The instrument was then administered to the training participants before and after the training. The Cronbach's alpha for the instrument for pre-test and post-test was 0.718 and 0.820, respectively, indicating acceptable internal consistency.

The shortened 17-item version of the original 51-item East Carolina University NP Self-Efficacy Scale by Leonard and Steele[9] was used to measure self-efficacy on HTN management. The Cronbach's alpha of the 17-item instrument was 0.93, indicating excellent internal reliability. To the knowledge of the researcher, no other published work had used this tool.

Data Analysis

The characteristics of the participants were described using frequencies, percentages, means, and standard deviations (SD). The effectiveness of the training program on the pre-test and post-test scores of the nurses in terms of knowledge and self-efficacy was determined using the paired *t*-test. All statistical analyses were done in IBM SPSS Statistics 23. A two-sided $P = 0.05$ is considered statistically significant.

Results

Participant Characteristics

Twenty-eight nurses answered the pre-test, while 24 participants completed the training program and answered the post-test, equivalent to a drop-out rate of 14.29% ($n = 4$). Most of those who completed the training program were females ($n = 16$, 66.7%), with a mean age of 32.42 years (SD = 8.397) and mean the clinical experience of 5.84 years (SD = 3.503).

Validation of HTN Training Modules

The expert panel determined that most of the learning objectives were covered adequately or moderately adequate by the module content. For Module 4 (Pharmacological Treatment), two comments were to include "working knowledge of how specific drugs act, based on the pathophysiology, and potential side effects" and to add "promotion of compliance." General comments for the entire module were as follows:

- Utilize varied teaching-learning strategies for the implementation of the program
- Attitudes are best seen in the teaching-learning strategies and not in the modules alone
- Outcomes cannot be evaluated by module alone
- Participants need a lot of practice since this was not the approach in past years
- Provide menu examples of high-salt and high-fat food.

These comments of the expert panel guided the further revision of the modules.

Effectiveness of HTN Training Program

Level of knowledge on HTN management

Before the training program, the total score of the participants on the knowledge instrument was 33.00 points (SD = 5.25). All participants got the correct answer on the following items: DASH diet, data clustering during the interview, smoking cessation and the 8th-Joint National Commission 8 lifestyle modification guidelines, obesity as a risk factor, and limiting the intake of processed foods. The top three items incorrectly answered by the participants were: Bruits, benefits of maintaining normal body mass index (BMI), BMI, quality improvement, and best strategy for BP >170/100.

After the training program, the total score of the participants was 43.08 points (SD = 43.08). This increase of 10.08 points (SD = 4.393) was statistically significant ($t = -11.245$, $P < 0.001$). Aside from the items above, all participants also got the correct answer on the following items: Target organ damage revealed by electrocardiogram (ECG), BMI, and side effect of ACE inhibitor. The top three items incorrectly answered by the participants were: Best strategy for BP >170/100, action for undiagnosed HTN, and health teaching on HTN.

Level of self-efficacy on HTN management

Before the training program, the participants' mean score on the self-efficacy instrument was 8.08 (SD = 1.16). The participants reported the highest score on the item, "Act ethically at all times," (M = 9.08) while the lowest score was on item, "Draw upon needs strengths and resources of the community to assist practice" (M = 6.88).

After the training program, the participants' mean score on the self-efficacy instrument was 9.06 (SD = 0.69). This increase of 0.98 points (SD = 0.77) was statistically significant ($t = -6.187$, $P < 0.001$). Similar to pre-intervention, the participants still reported the highest and lowest scores on the same items (M = 9.54 and M = 8.42, respectively).

Discussion

Validation of HTN Training Modules

An important comment on the training modules was regarding Module 4, on pharmacologic treatment of HTN, perhaps

since this competency was new to the APN participants in the Philippines. One of these clinical competencies in which APNs differ from RNs includes the legal privilege and authority to prescribe medicines.

An expanded role of APNs involves diagnostics and medication management. In this study, the APNs were able to prescribe and titrate medications with a goal of achieving target BP for each client using well-defined protocols based on national treatment guidelines in collaboration with the physician. Nurse-led HTN management has been demonstrated to result in greater rates of BP control than those achieved with standard care.[10] These improved outcomes resulted from APNs placing a greater number of clients on medications, changing drug regimens in response to inadequate BP control, and placing a higher proportion of clients on multiple drug regimens to achieve target BP control.

Effectiveness of HTN Training Program

During the 32-h training program for APNs on HTN management, as previously discussed the improvements in the participants' knowledge and self-efficacy were statistically significant. Item analysis of the participants' performance on the knowledge scale revealed that questions on health education and lifestyle interventions were most frequently answered correctly, while those on therapeutic or medical decisions were frequently answered incorrectly. In contrast, the participants reported the highest self-efficacy scores on "acting ethically," while the lowest scores were on "drawing upon community strengths and resources."

Similar to this study's results, nurses in Ghana, West Africa, underwent a task-shifting strategy for hypertension (TASSH) training to see its effect on their knowledge and practice on HTN control and management.[11] With a total of 64 nurses who attended TASSH training, there was a significant increase in nurses' knowledge and practice concerning HTN screening and management based on the results from pre- and post-training assessments. Twenty-seven percent (26.9%) of the nurses scored 80% or more on the HTN knowledge test at pre-training assessment. This score improved significantly to 95.7% post-training. In addition, nurses also stated that improvement of interpersonal skills and patient education was considered as positive outcomes of participation in the training.

A retrospective survey conducted in 2004 revealed that new NPs on completion of their initial NP program perceived themselves to be most prepared in the areas of "health assessment," "differential diagnosis," "pathophysiology," "pharmacology," "health teaching," and "management of acute cases."[12] On the other hand, they reported a feeling of being least prepared for "ECG and radiology interpretation," "microscopy," "mental illness management," billing and coding," and "simple office procedures." The NPs are better known for their noteworthy nurse-patient relationship and patient-centered care[13] on top of their safe and effective primary care which have been proven by several studies to be comparable and even superior to physician-led care for some measures.[14]

A cross-sectional survey[15] in a state where NPs seek mutual agreement with collaborating physicians revealed that age and years of experience of NPs are not associated with the NPs' perception of the level of autonomy, reflecting self-efficacy for independent practice and promotion of interprofessional collaboration.

Conclusion and Recommendations

The validated HTN training program module was effective in equipping the masters-prepared nurse with the required knowledge, skills, and self-efficacy in providing entry-level APN care for patients with primary HTN. On an expert review of the training program, the seven-part module addressed the learning outcomes adequately, identified from the competencies outlined by the NONPF in the United States. The investigator-developed scale to measure the nurses' knowledge of HTN management had excellent content validity and acceptable reliability.

It is highly recommended that a bigger sample size of nurses undertake the training program and a stronger research design be used to strengthen the research evidence on its validity and outcomes. Furthermore, it is recommended that the competencies included in the training program modules be integrated into the country's master's degree curriculum in Adult Health Nursing, to provide adequate preparation for entry-level APN care.

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Original Article

Effect of Beta-blockers on Hypertension and Heart Failure with Reduced Ejection Fraction: A Systematic Review of Randomized Controlled Trials

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Abstract

Background: Beta-blockers have long been used as the treatment for hypertension (HTN) with comorbidities such as heart failure (HF), angina, and myocardial infarction. Numerous clinical trials showed the effects of beta-blockers to prolong life and to relieve symptoms. In particular, four particular beta-blockers – namely metoprolol, carvedilol, bisoprolol, and nebivolol, have been shown to have salutary effects in HF patients. **Objectives:** We evaluated the effects of these four beta-blockers in patients with HTN and HF with reduced ejection fraction (HFrEF). **Methods:** We carried out a systematic literature search in PubMed and Cochrane for randomized controlled trials on the use of beta-blockers in HTN and HFrEF in reducing hospitalization, morbidity, and mortality. **Conclusion:** The beneficial effects of metoprolol, carvedilol, bisoprolol, and nebivolol primarily stem from their attenuation of sympathetic nervous system (SNS) activity that prevents further cardiac structural changes and dysfunction, as seen in relation to uncontrolled HTN. However, other effects such as antioxidant and anti-endothelin effects possessed by carvedilol and the enhanced secretion of nitric oxide with nebivolol are also being attributed to having protective and beneficial outcomes on HF patients.

Keywords: Adrenergic beta-blockers, beta-antagonists, beta-blockers, bisoprolol, carvedilol, congestive heart failure, hypertension, metoprolol, nebivolol

Research Question

Among adults with hypertension (HTN) and heart failure (HF) with reduced ejection fraction (HFrEF), how effective are beta-blockers in reducing the rates of hospitalization, morbidity, and mortality? [Figure 1].

Significance of the study

With the current guidelines in the management of HTN with HFrEF, there is no specific recommendation, on which particular beta-blocker is recommended. With this study, the researchers aimed to be able to recommend which specific beta-blockers can be recommended in HTN with HFrEF patients.

Objectives

General objective

The general objective of this study was to evaluate the effects of the different beta-blockers in patients with HTN and HFrEF.

Specific objectives

The specific objectives of this study were as follows:

- To discuss the pathophysiologic mechanisms behind the development of HTN and HF
- To determine which beta-blockers are effective in reducing rates of hospitalization, morbidity, and mortality among hypertensive patients with HFrEF.

Materials and Methods

Study selection

The authors searched for randomized control trials on PubMed Database and Cochrane central register of controlled trials. The following keywords were used: HTN, HF, congestive HF (CHF), beta-blockers, adrenergic beta-blockers, and beta-antagonists. Particular studies were selected according to the set inclusion criteria.

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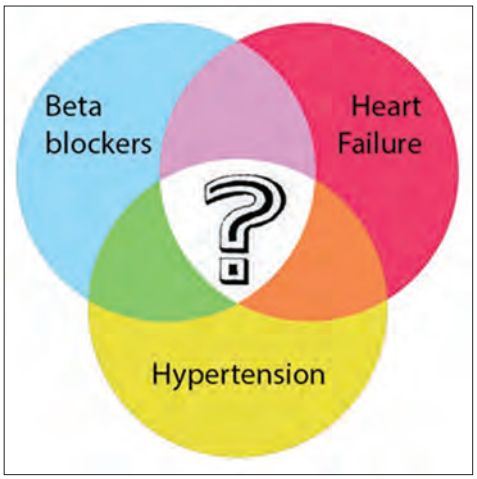

Figure 1: The research question probes the effectivity of beta-blockers in adults with hypertension with concomitant HF

Inclusion criteria

The researchers included studies fulfilling all of the following criteria:

- Randomized
- Controlled with placebo or active treatment agents
- Double or single blinding
- Diagnosis of HTN and HFrEF in the study group
- Published in PubMed or Cochrane within the past 50 years.

Background of the Study

Pathogenesis of HTN

The maintenance of a normal arterial blood pressure (BP) is essential for organ perfusion. This involves a number of physiological mechanisms primarily the plasma volume, autonomic nervous system, and renin-angiotensin-aldosterone system.[1] In cardiovascular physiology, BP is determined by the product of cardiac output (CO) and total peripheral resistance (TPR).

$$BP = CO \times TPR \qquad \text{Equation (1)}$$

Derangements in said mechanisms, along with genetic and environmental factors, result in HTN, which is characterized usually by a normal CO and an increased TPR.[2] In early HTN, however, TPR is not increased but due to the sympathomimetic overactivity, the BP goes up. There is an increased CO to which the rise in TPR acts as a response to prevent transmission of high pressure to the capillary bed that could cause cell apoptosis. If left untreated, TPR is further increased, resulting to increased pressure load and trophic effects such as volume load and growth factors such as catecholamines and angiotensin II.[2]

HTN and HF

HTN is considered the second most common risk factor in the development of HF, alongside myocardial infarction (MI).[3] The former is considered pertinent due to its worldwide prevalence and a three-fold increase in risk for the development of HF.[4] In the case of uncontrolled and long-standing HTN, the decrease in CO and thus development of HF is brought about by increase in afterload and a decrease in venous capacitance.[5-7] Chronic HTN then causes pressure-mediated cardiac remodeling with the left ventricular hypertrophy (LVH), left ventricular stiffness, and ultimately diastolic dysfunction.[8] Consequences of LVH can lead to cardiomyopathy with reduced myocardial contractility and impaired cardiac reserve and cardiac arrhythmias (single premature contractions and dysrhythmias),[9-11] all of which cause further decrease in CO and worsening of HF [Figure 2].

While MI and HTN are separate risk factors for HF, there is a link between the latter and MI, due to the high frequency (30–40%) of associated coronary risk factors such as dyslipidemia, diabetes, smoking, and obesity observed in hypertensive patients.[4]

History of beta-blockers

Beta-blockers remain to be the most widely used therapeutic drug in both non-cardiac and cardiac conditions. It was first introduced into clinical medicine in 1964 by Sir James Black and approved by the US Food and Drug Administration in 1973 for the treatment of angina.[12,13] Since then, a myriad of beta-blockers has been available in the market as part of a physician's armamentarium in treating cardiovascular diseases, particularly HTN and HF.

Types of beta-blockers

Beta-blockers are divided into two main categories: Beta-1 selective blockers and non-selective beta-blockers (with effects to beta-2 receptors). Two studies by Wong and Wright depicting efficacy of both beta-1 selective blockers and non-selective beta-blockers have shown to be able to reduce BP compared to placebo, but their results are not significant with each other.[14,15]

As deduced from Table 1, four of 20 beta-blockers seen in this study are mainly used in the management of HF.

Pharmacologic properties of beta-blockers

Blockade of beta-adrenergic receptors (AR) fundamentally interferes with the sympathetic regulation of the heart by mediating the effects of catecholamines (e.g., norepinephrine and epinephrine). At rest, beta-blocker administration minimally affects heart rate and contractility, but on exertion, it significantly suppresses the increase in heart rate and contractility induced by exertion [Figure 3].[17] There are at least three distinct types of beta receptors: beta-1, beta-2, and beta-3.[18,19] The stimulation of beta-1 receptors found in heart muscle, increases heart rate, contractility and atrioventricular conduction, and decreases AV node refractoriness. Stimulation of beta-2 receptors found in heart muscle but more prominent in bronchial and peripheral vascular smooth muscle, vasodilates the blood vessels, and bronchodilates the lungs. Beta-3, found in adipose tissue and heart muscle, may reduce cardiac contractility and mediate catecholamine-induced thermogenesis, i.e., by utilization of brown adipose tissue.[20,21]

Table 1: Types of beta-blockers[16,17]

Drug	Adrenergic receptor blocking activity	Intrinsic sympathomimetic activity (partial agonist)	Membrane stabilizing activity	Congestive heart failure (reduced ejection fraction)
Acebutolol	B1	+	+[2]	–
Alprenolol	B1 and B2	+	+	–
Atenolol	B1	–	–	–
Betaxolol	B1	–	+	–
Bisoprolol	B1	–	–	+
Bupranolol	B1 and B2	–	–	–
Carteolol	B1 and B2	++	–	–
Carvedilol	B1, B2, and A1	–	++	+
Celiprolol	B1	+	–	–
Esmolol	B1	–	–	–
Labetalol	B1, B2, and A1	+	±	–
Metoprolol	B1	–	±[2]	+
Nadolol	B1 and B2	–	–	–
Nebivolol	B1	–	–	+
Oxprenolol	B1 and B2	+	+	–
Penbutolol	B1 and B2	+	–	–
Pindolol	B1 and B2	+++	±	–
Propranolol	B1 and B2	–	++	–
Sotalol	B1 and B2	–	–	–
Timolol	B1 and B2	–	±	–

(-) No activity [1]Inhibits B2-receptors (bronchial and vascular) at higher doses. (+) Low Activity [2]Only detectable at higher doses than needed for Beta-blockade. ++ Moderate activity. +++ High activity. ± No/low activity

In a non-failing heart, 80% of the expressed adrenoreceptors are beta-1 and 20% are beta-2; the ratio becomes almost equal in a failing heart when beta-1 receptors are downregulated correlating with the severity of the heart disease.[21] On the other hand, myocardial beta-3 receptors, present both in the atria and ventricles, are overexpressed in HF and HTN [Figure 4].[22] Stimulation of beta-3 receptors may decrease cyclic adenosine monophosphate (cAMP) generation, thereby reducing cardiac contractility, which is in contrast to the stimulation of beta-1 and beta-2 receptors that increase cAMP levels. Despite the potential for beta-receptor exploitation for many heart disease, for all practical purposes, so far, beta-1 and beta-2 receptor blockers have been the only target for clinical application [Table 2].[23]

There have been recent studies that aim to prove the importance of beta-3 overstimulation in HF patients and its importance in providing a "break in inotropic stimulation."[24] This still newly studied mechanism of β3-AR stimulation involves the use of nitric oxide (NO) release through NO synthase activation, with its mechanism still unclear.[25] As discussed earlier, β3-AR is upregulated in failing hearts in both human and animal models. According to Cannavo and Koch, beta-blocker usage helps in blocking the effects of catecholamines and prevents further β1 and β2-ARs downregulation, while increasing the activity of β3-ARs.

Table 2: Novel mechanisms of selected beta-blockers that may have an effect in reducing the effects of heart failure with reduced ejection fraction in hypertensive patients[28-30]

Beta-blocker	Beta-3 adrenergic receptor action	Generation of NO
Metoprolol	Upregulation	Yes
Carvedilol	Downregulation	No
Nebivolol	Upregulation	Yes
Bisoprolol	No	No

NO: Nitric oxide

Further studies are being underway to determine the specific properties of currently used beta-blockers in the market and if there are any changes to β3-AR utilization.[26] A study by Zhao *et al.* showed that metoprolol (selective β1-blocker) showed no change in β3-AR yet small doses of the same drug are shown to improve long-term outcomes in patients with CHF, while carvedilol (non-selective β1-blocker) showed β3-AR downregulation.[27] A study by Sharma *et al.*, however, showed the use of metoprolol in improving cardiac function by enhancing the β3-AR upregulation and NO generation.[28] Nebivolol in recent years has also showed activated cardiac β3-ARs, leading to a significant reduction of infarct size and reduce cardiac fibrosis and apoptosis.[29,30]

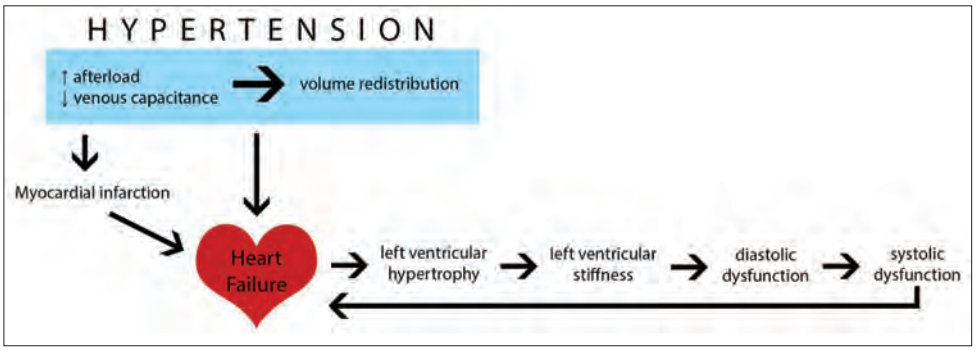

Figure 2: Graphic representation of how hypertension would lead to heart failure and subsequent negative effects

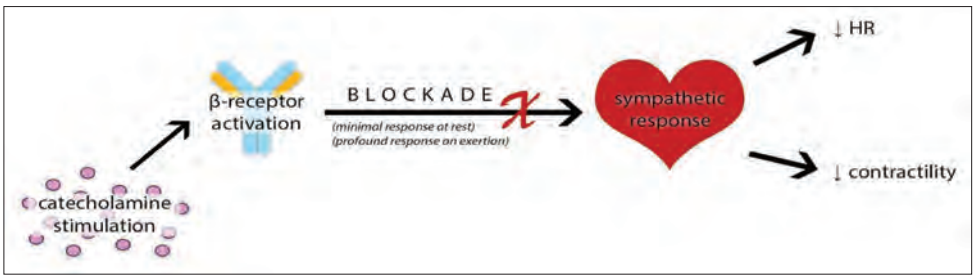

Figure 3: Manifestation on how catecholamine blockade though its receptor would lead to the blunting of sympathetic response of the heart

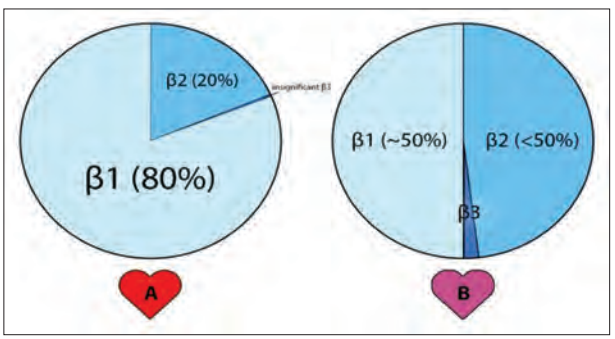

Figure 4: The pie graph represents the theoretical amount of beta-receptors in a normal heart (a) and a diseased heart (b) note that in a diseased heart, the number of beta-1 and beta-2 receptors are close to equal, with detectable values of beta-3 receptors[24]

In a study by Cleland *et al.*, wherein 11 randomized multinational clinical studies were evaluated for the treatment of HF, it was found out that beta-blockers improve left ventricular systolic function and reduce cardiovascular morbidity and mortality for patients with HF and left ventricular ejection fraction (LVEF) of < 40% in sinus rhythm; however, the said benefits are not seen for patients with LVEF of >/= 50%.[31]

Metoprolol

Metoprolol, initially marketed in 1967, is a beta-1 selective antagonist and is one of the known beta-blockers to have proven benefit when given in HF patients, along with bisoprolol and carvedilol. It was found to have a protective effect on sudden death in hypertensive patients as well as prevention of sudden death post-MI primarily through its antifibrillatory effect. This improved beta-blockade may confer some protection to the disappearance of vagal tone and sudden sympathetic nervous system (SNS) activity that causes ventricular fibrillation and therefore sudden death.[32] There are only two studies which have evaluated the efficacy of beta-blockade with survival being the predefined endpoint in HF. These are the Metoprolol CR/XL Randomized Intervention in CHF (MERIT-HF) study and the Cardiac Insufficiency Bisoprolol Study II (CIBIS II). The two beta-blockers in the said studies are both lipophilic and are highly beta-1 selective antagonist. Looking at the results of these two studies, death due to worsening of the HF was significantly decreased with beta-1 blockade.[33]

Bisoprolol

Similar salutary effects in HF were shown in the CIBIS II trial, wherein the positive effect of bisoprolol, initially marketed in 2000, was demonstrated on all-cause mortality. This was primarily attributed to its antiarrhythmic effect through prevention of alteration in cardiac structure and function, which is seen in hypertensive patients as indicated by having progressive increase in the left ventricular mass and decline in CO as the disease progresses. Theoretically speaking, blockade of both beta-1 and 2 adrenoreceptors should confer better cardiac protection and prevention of arrhythmia through inhibition of catecholaminergic effects. However, it was found that blocking beta-1 receptors are enough to prevent fatal arrhythmia and ultimately decrease the rate of sudden death.[34]

Carvedilol

Carvedilol, marketed in 1995, is unlike bisoprolol and metoprolol since it blocks both beta-1 and beta-2 receptors, as well as alpha-1 receptors. This added blockade can provide additional benefit in preventing adverse outcomes of the SNS through the noradrenergic mechanisms. This added blockade was shown to have favorable outcomes in patients who are classified to be in New York Heart Association Functional Class III or IV. A possible explanation is that carvedilol, aside from having additional adrenergic blocking activities, also has antioxidant activity and anti-endothelin effects which can attenuate the SNS effects on the circulatory system. In a study evaluating the efficacy of carvedilol on survival in patients with severe chronic HF, the investigators have shown that previously reported salutary effects of carvedilol on morbidity and mortality in patients with mild-to-moderate HF were again noted in patients with severe HF enrolled in this trial.[35]

Nebivolol

Nebivolol, marketed in 2008, has peripheral vasodilating properties mediated by the modulation of the endogenous production of NO, thereby causing endothelium-dependent relaxation. It acutely lowers BP and reduces peripheral vascular resistance with an increase in stroke volume but without compromising left ventricular function. HTN is characterized by progressive stiffening of the ventricle that leads to diastolic dysfunction or HF, and nebivolol plays a central role by causing higher diastolic peak filling rates which means that there is more ventricular distensibility and relaxation that causes improved CO.[36]

Particularly in HF secondary to coronary artery disease, nebivolol decreases BP and heart rate through beta-1 blockade that is then compensated by an increase in stroke volume. Another novel characteristic of nebivolol is that it protects blood vessels from atherosclerosis by significantly increasing wall distensibility and compliance. In the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with HF (SENIORS), wherein patients of age >70 years with HF were enrolled, regardless of the initial ejection fraction, a decreased rates of mortality and morbidity were demonstrated.[37]

Conclusion

The beneficial effects of metoprolol, carvedilol, bisoprolol, and nebivolol primarily stems from their attenuation of SNS activity that prevents further cardiac structural changes and dysfunction, as seen in relation to uncontrolled HTN that causes LVH and impaired CO. However, other effects such as antioxidant and anti-endothelin effects possessed by carvedilol, and the enhanced secretion of NO with nebivolol is also being attributed to having protective and beneficial outcomes on HF patients.

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Review Article

Treatment of Hypertension in the Different Stages of Chronic Kidney Disease

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Abstract

The blood pressure (BP) targets for patients with chronic kidney disease (CKD) to decrease the risk of cardiovascular outcomes and progression of renal disease remain unclear. In 2012, the Kidney Disease: Improving Global Outcomes (KDIGO) published a clinical practice guideline on the management of BP in CKD patients not on renal replacement therapy, for both diabetic and non-diabetic population. KDIGO recommended the target BP of <140/90 mmHg for CKD patients without albuminuria and <130/80 mmHg for those with albuminuria. Since then, new data arising from recent clinical trials such as the 2015 Systolic BP Intervention Trial have added to the evidence base. As well as, the current recommendations from the American College of Cardiology/American Heart Association Clinical Practice Guideline in 2017 have made us reevaluate our BP targets and hypertension management in the CKD population.

Key words: Albuminuria, blood pressure, chronic kidney disease, dialysis, hypertension, renal replacement therapy

Introduction

Hypertension (HTN) is the chronic elevation of blood pressure (BP) sufficient to increase the risk of HTN-mediated organ damage and other related complications in the general population, particularly in the presence of comorbidities.[1-4] It is the level of BP at which the benefits of lifestyle interventions or medical therapy outweigh the risks of treatment.[5] In 2015, the global prevalence of hypertension (HTN) was estimated to be 1.13 billion.[6] There is around 30–45% of adults worldwide diagnosed with HTN. Majority of those diagnosed with elevated BP are males. This is consistent across different countries regardless of socioeconomic status.[7] The aging population, sedentary lifestyles, and obesity contribute to the rise of HTN cases globally, with an estimated increase in disease prevalence to close to 1.5 billion by 2025.[8]

Interdependence of HTN and CKD

Chronic kidney disease (CKD) comprises a range of different pathophysiologic processes, leading to progressively irreversible decline in estimated glomerular filtration rate (eGFR) over 3 months that have a great impact to overall health. Different stages of CKD have been defined based on the eGFR. The two main causes of CKD worldwide are diabetes and high BP.[9]

The pathogenesis of HTN in CKD is an actual interplay of independent and interdependent mechanisms, where the kidney is both a contributor and the target organ. The relationship of HTN and CKD has been well established in several literatures.[10] The dilemma to identify whether the HTN caused the kidney disease or the other way around could be challenging. Regardless of which came first, the degree of HTN among patients with kidney disease usually worsens with the severity of renal dysfunction. Kidney involvement in HTN is based on the findings of renal parenchymal changes, declines in kidney function with or without the presence of albuminuria that is independent predictors of increased cardiovascular (CV) risk and renal disease progression.[11] All hypertensive patients with suspected kidney involvement should have an annual examination consisting of serum creatinine, eGFR, and urine albumin-creatinine ratio (UACR).[1]

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HTN in patients with CKD across all stages can be produced by several mechanisms including volume expansion, abnormalities in renin secretion, and hyperactivity of the autonomic nervous system.[12]

BP Target in CKD Patients

The primary goal in the management of HTN in CKD is to lessen CV events and delay the progression to end-stage renal disease (ESRD) that necessitates renal replacement therapy or kidney transplantation.[13] However, the optimal BP level in the management of HTN in the CKD population remains uncertain despite the recent and robust source of trial data and clinical guidelines.[2,14] The threshold for treatment has been continually refined as new research accumulates [Table 1].

It is also important to note that the type of BP measurement and monitoring for CKD patients are major factors to be considered in the HTN in CKD treatment strategy. Home BP measurements which correlate closer to ambulatory BP monitoring are superior to conventional office BP measurements and are hence more predictive of CV outcomes.[15,16]

Focusing on the reduction of CV events, studies on both diabetic and non-diabetic patients with kidney disease have been facilitated throughout the years. The Action to Control CV Risk in Diabetes trial enrolled diabetic patients with mild CKD (creatinine <1.5 mg/dl) and subjected to an intensive systolic BP (SBP) goal of <120 mmHg versus a standard BP goal of < 140 mmHg. There was a reduction of CV events in the diabetic patients, but this effect is small and statistically insignificant.[17] A follow-up study also shows increased risk of adverse event associated with the intense BP-lowering strategy. Clinical studies on the non-diabetic CKD population also failed to show benefit of lowering BP thresholds to <130/80 mmHg compared to <140/90 mmHg in slowing CKD progression or significant impact on mortality or CV outcomes.[18-21]

Albuminuria has been a focal point in defining intensity of BP-lowering strategies and published guidelines have exhibited disparities in BP goals for CKD patients. In 2012, the Kidney Disease: Improving Global Outcomes (KDIGO) recommended the <130/80 mmHg target only for those with proteinuric CKD (ACR ≥30 mg/g).[1] The JNC-8 (2014) reports recommended BP of 140/90 mmHg, regardless of proteinuria.[22] Based on the American College of Cardiology/American Heart Association (ACC/AHA) BP guidelines of 2017, the BP goal of <130/80 mmHg is a Class 1 recommendation in adults with CKD, regardless of albuminuria.[3]

The SBP Intervention Trial (SPRINT) studywas designed to measure the hypothesized difference in clinical outcomes of standard BP control (SBP < 140 mmHg) versus intensive BP lowering (SBP <120 mmHg).[2] To date, the study is considered to be the biggest randomized trial (n = 9361) that evaluates the different BP targets on CV and renal outcomes in the non-diabetic, hypertensive population. The trial was prematurely terminated because the results showed that intensive BP-lowering decreased the risk of CV disease by 25% and the risk of all-cause mortality by 27%. However, there was an increased risk of syncopal attacks, decline in eGFR, and electrolyte abnormalities with intensive BP lowering.

About 28% (n = 2646) of the total SPRINT cohort was diagnosed with CKD at baseline. The primary composite CV outcome was similar in patients who were treated with intensive and standard BP lowering (hazard ratio 0.81; 95% confidence interval [CI], 0.63–1.05) after a median follow-up of 3.3 years. The composite outcome of ≥50% decrease in eGFR from baseline or occurrence of ESRD was no different from both treatment groups (HR, 0.90; 95% CI, 0.44–1.83). Furthermore, no significant difference was seen on the incidence of adverse events between the treatment and control group.[23]

More recently released 2018 ESC/ESH Guidelines have taken the overall results of SPRINT into consideration. Addressing the issue of hypertensive patients with CKD (diabetic or non-diabetic), it is recommended to lower SBP to a range of 130–139 mmHg and that "individualized treatment" should be based on tolerability, impact on renal function, and electrolyte changes.[24]

In patients with ESRD on maintenance dialysis, the pathogenesis of HTN is multifactorial and is confounded by a wide array of risk factors. The high-risk nature of these patients makes them often excluded in major clinical trials on intensive versus standard BP control. Thus, the optimal BP targets of these patients are still not established. The KDOQI guidelines have previously recommended a target SBP of <140 mmHg and SBP <130 mmHg, pre- and post-hemodialysis (HD), respectively, this is largely based on expert opinion.[25] While there is a decrease in mortality noted in the general population with intensive BP control, observational studies on HD patients have noted an increase in mortality among those with SBP ≤140 mmHg, among elderly patients and those with diabetes.[26-31]

Drug Therapy

The renin-angiotensin-aldosterone system (RAAS) is recognized as the best modulator of BP and a determinant of HTN-mediated organ damage. Angiotensin II is the main effector of the RAAS that increases the vascular tone of the glomerular arterioles (afferent and efferent) in *in vivo* studies.[32] Due to these changes, it is able to regulate the glomerular capillary pressure and filtration rate. Angiotensin II predominantly causes a vasoconstrictor efferent glomerular arterioles, leading to an increase in filtration fraction and glomerular hydraulic pressure. There is also an observed disruption on the size selectivity of the plasma proteins to the glomerular barrier.[33] These changes lead to intracapillary HTN and increased ultrafiltration of plasma proteins that contribute to the onset of kidney disease and worsening of renal function.

The use of RAAS blockers, such as angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARB), has been the foundation of the treatment of elevated BP in patients with CKD with the additional benefit of slowing CKD progression and protection from CV outcomes. These have been supported by several studies in both the diabetic and non-diabetic population with kidney disease.[34-36]

Table 1: Guidelines from various target blood pressure recommendations for patients with chronic kidney disease

CKD stages and presence of albuminuria	KDIGO (2012)	JNC-8 (2014)	ACC/AHA (2017)	ESC/ESH (2018), SBP
CKD stages 1–5 with albuminuria	<140/90	<140/90	<130/80	130–139
CKD stages 3–5 without albuminuria	<130/80	<140/90	<130/80	130–139

KDIGO: Kidney Disease: Improving Global Outcome, JNC-8: Eighth Joint National Committee, ACC/AHA: American College of Cardiology/American Heart Association, ESH: European Society of Hypertension, ESC: European Society of Cardiology, SBP: Systolic blood pressure, CKD: Chronic kidney disease

Table 2: Suggested antihypertensive medication in chronic kidney disease patients (predialysis and dialysis) and their prescribing order

Prescribing order	CKD (predialysis)	Dialysis patients
First	ACEi or ARB	ARB
Second	CCB	Beta-blockers (consider as first line for patients with established CV disease or at high risk)
Third	Diuretics	CCB

CKD: Chronic kidney disease, ACEi: Angiotensin-converting enzyme inhibitor, ARB: Angiotensin II receptor blocker, CCB: Calcium channel blocker, CV: Cardiovascular

Dual RAAS blockade was previously believed to be more beneficial for both CV and renal outcomes as this would lead to a more extensive inhibition of angiotensin II production. Unfortunately, based on the results of the ONTARGET (Telmisartan, ramipril, or both in patients at high risk for vascular events trial)[37] and ALTITUDE (Cardiorenal end points in a trial of aliskiren for Type 2 diabetes),[38] there were more adverse events seen in the combination therapy such as an increased risk of hypotension, renal dysfunction, and hyperkalemia, with no additional benefit as compared to the controls.

There is currently a lack of strong evidence to support one drug class over another in the management of HTN in the dialysis population. The choice of antihypertensive therapy should be tailored to the individual patient basing on effective and safe BP lowering, CV protection, and consideration of drug pharmacokinetics altered by dialysis treatment.

In ESRD patients, ACEis and ARBs are effective at lowering BP.[39,40] They are often recommended as first-line antihypertensive therapy for patients on dialysis basing on their trends on CV benefits seen with their use in the general population.[41] It is important to consider that the choice of ACEis and ARBs is not interchangeable for dialysis patients, as there are important differences between in their important pharmacokinetic differences to be considered, particularly on renal clearance and drug removal during dialysis. Most ARBs are not dialyzed during conventional dialysis and may be preferred in these patients for sustained BP reduction [Table 2].[42]

There are clinical trials that support the evidence that beta-blocking agents can provide the CV protection seen in the general population even to dialysis patients.[43,44] Aside from their effects on addressing the overactivation of the sympathetic nervous system in hypertensive dialysis patients, they may have the potential benefit on CV protection through nitric oxide-induced vasodilation and antioxidant properties.[45] One of the studies to investigate this protective effect was a prospective, placebo-controlled trial with carvedilol. In this 2-year study, echocardiographic evidence showed a significant attenuation of pathologic remodeling of the left ventricle and higher ejection fractions in the treatment group compared to the placebo group. Furthermore, there were fewer hospital deaths recorded and hospitalization rates in the treatment group.[43] A meta-analysis done in 2019 which included three randomized controlled trials (comparing β-blockers vs. placebo or another HTN drug) showed a significant association between β-blockers and reduced all-cause mortality, CV mortality, CV events, or hospitalizations among the 363 dialysis patients included in the studies analyzed.[46]

An alternative antihypertensive drug in the management of HTN in CKD is the calcium channel blockers. They provide good BP lowering and are well-tolerated antihypertensive medications.[45] Large trials specifically examining CCBs for HTN in CKD are lacking, but these drugs have often been used as an active comparator in landmark trials of ACEi and ARBs in CKD.[19,34] They are effective antihypertensive agents in both CKD and ESRD.[46]

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Current and Emerging Concept

Management of Hypertension in the Setting of Acute Stroke: A Literature Review

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Abstract

Stroke is still a highly prevalent complication of hypertension and cause of death in the Philippines and in the rest of Southeast Asia. Management of acute elevation of the blood pressure (BP) can be a challenge which can impact both short- and long-term outcomes. The dilemma of allowing or not some degree of "permissive hypertension" in an acute stroke is a question every clinician is confronted with. This paper aims to summarize the recent guidelines on BP management in the setting of acute stroke based on the recommendations of three international guidelines, namely the American College of Cardiology/American Heart Association (ACC/AHA), European Society of Cardiology/European Society of Hypertension (ESC/ESH), and the Canadian Stroke Best Practices. It also reviews the major randomized controlled trials and other publications evaluating the management of BP elevation in an acute stroke setting. The updated guidelines in the ACC/AHA, ESC/ESH, and Canadian best practice have no significant difference in their recommended BP threshold for intervention. In general, BP lowering is not recommended unless BP is ≥220/110 mmHg. However, in patients who are eligible for intravenous (IV) thrombolysis and have very high systolic BP (SBP) ≥185 mmHg or diastolic BP ≥110 mmHg, cautious BP lowering should be done before IV thrombolysis and should be maintained during the treatment duration. In the acute BP management of intracerebral hemorrhage (ICH) earlier guidelines favored lowering of BP to <140 mmHg, SBP based on a large randomized controlled trial – the Intensive BP reduction in acute cerebral hemorrhage (INTERACT) trial 2. On the other hand, outcomes of the antihypertensive treatment in ATACH-2 trial showed a significantly higher rates of neurological deterioration within 24 h in those with reduced and renal events and pneumonia was higher in the group where intensive BP management was instituted. In general, clinical practice guidelines advocate that in those with acute ICH and SBP between 150 and 220mmHg, reducing SBP to <140 mmHg within 6 h is not beneficial in terms of death and functional outcome and can be potentially harmful. In acute ICH and SBP >220 mmHg, it is reasonable to lower BP with IV therapy to around 180 mmHg.

Key words: Hypertension management in acute stroke, permissive hypertension, spontaneous intracerebral hemorrhage

Introduction

The burden of stroke has not been mitigated over the past 2–4 decades. In terms of the proportions of disability and mortality as a result of stroke, the less developed regions of the world surpass most developed nations.[1] The primary causes of the increased global burden of stroke are related to the increase in stroke risk factors, particularly hypertension. Part of the reason for the higher disability and mortality rates is probably in the lack of understanding on how best to manage the blood pressure (BP) in different stroke settings.[2,3]

In general, acute ischemic strokes (AISs) account for 80% of the stroke cases while hemorrhagic strokes account about 20% depending on the specific population. Recent data from the Risk Factors for Ischemic and Intracerebral Stroke in 22 Countries (INTERSTROKE) study, which included the Philippines, China, Malaysia and Sudan showed that the proportions of ischemic and

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hemorrhagic stroke in Southeast Asia were about 78% and 22%, respectively, compared to about 91% of ischemic stroke and 9% of hemorrhagic stroke in high-income countries.[4,5]

How to manage the elevated BP in these two conditions in the acute setting is challenging in clinical practice, and this has been tackled by various guidelines over the last several years.[6] Understanding the principles of BP management in acute stroke according to the best evidence based on the latest and better-designed research outcome results are important. However, in certain circumstances, an individualized approach to the BP management on a specific stroke patient may be necessary.

While the guidelines on BP management in AIS are fairly uniform in most guidelines, this has been challenging in hemorrhagic strokes. Spontaneous, non-traumatic intracerebral hemorrhage (ICH) still is a major reason of morbidity and mortality across all countries. Even though ICH has been behind in terms of clinical trials that will help in the management as compared to other types of strokes (ischemic and subarachnoid hemorrhage), there was a significant increase of researches regarding ICH in the past decades.

The recent guidelines in BP management of acute stroke in the acute setting are reviewed here. Review of some recent clinical trials, not included or reviewed in the current guidelines were also analyzed.[7-11]

BP Management in AIS

Acute hypertension management in the setting of an AIS is as important as giving intravenous (IV) thrombolysis or initiating antithrombotic agents. There are several studies and guidelines that discuss management of elevated BP in AIS. Recommendations depend on the following: Whether or not patients are eligible for thrombolysis or not, presence of comorbid conditions, and presence of hypotension.

In the 2018 American Heart Association (AHA)/ASA Guidelines for the Early Management of Patients with AIS,[12] for patients not eligible for IV thrombolysis, acute BP lowering is not recommended unless the BP is ≥220/110 mmHg. Exceptions are patients who have comorbid conditions that require lowering of BP. Starting or restarting management of hypertension for the first 48–72 h post-ictus is not successful to avoid death or dependency. For those who are eligible for IV thrombolysis and who have very high BP (>185 mmHg systolic blood pressure [SBP] or >110 mmHg diastolic blood pressure [DBP]), BP should be cautiously reduced to an SBP of <185 mmHg and DBP to <110 mmHg before initiating IV fibrinolytic therapy. For those patients, that is, for possible intra-arterial therapy and for those who were not given IV thrombolytic therapy, it is acceptable to sustain BP ≤185/110 mmHg before the procedure.[12]

During the first 24 h post-ictus, it is acceptable to decrease BP by 15%. However, there are no concrete evidence existing in terms of medication selections for BP lowering. Initiating or reinitiating BP lowering agents during admission in patients with BP >140/90 mmHg who are neurologically stable are harmless and are acceptable to achieve better long-standing BP control not unless contraindicated. It is also necessary to avoid and correct hypotension and hypovolemia to ensure adequate systemic circulation essential for maintenance organ function.[12]

In the 2018 Canadian Recommendations for Acute Stroke Management, similar BP recommendations are given to ischemic stroke patients eligible for thrombolytic therapy.[13] Markedly elevated BP >185/110 mmHg should be managed before IV thrombolysis to lower the possibility of hemorrhagic conversion. BP should be lowered and sustained <185/110 mmHg before alteplase therapy and <180/105 mmHg within the next 24 h after giving alteplase. In patients with ischemic stroke not qualified for thrombolysis, acute BP lowering is not recommended. Extreme BP elevation (e.g., SBP >220 mmHg or DBP >120 mmHg) must be managed accordingly to lower down the BP by around 15%, and not >25%, within the first 24 h with additional steady lowering afterward to desired level for continuing secondary stroke prevention, although the ideal BP level to reach and maintain in the hyperacute phase is unknown at this time. It is a good practice to avoid rapid or excessive lowering of BP because this may aggravate present cerebral ischemia specifically in patients with intracranial or extracranial arterial obstruction.[13]

In the 2018 European Society of Cardiology/European Society of Hypertension (ESC/ESH) Guidelines for the treatment of hypertension in AIS, regular BP lowering is not advocated with the following exceptions: (a) Patients with AIS who are candidates for IV thrombolysis, BP must be judiciously reduced and sustained at <180/105 mmHg within the first 24 h after IV rTPA and (b) patients with significantly elevated BP who were not given IV rTPA, BP lowering agent may be contemplated, based on clinical judgment, to lower down BP by 15% within the first 24 h post-ictus.[14] A comparative summary of the hypertension management in the acute setting recommendations from three different guidelines is shown in Table 1.

In the 6th edition of the Stroke Society of the Philippines (SSP) Handbook for Stroke Prevention, Treatment, and Rehabilitation in 2014, it is recommended treating with an antihypertensive agent if mean arterial pressures (MAPs) are >130 mmHg, avoiding a precipitous drop in BP (not >15% of baseline MAP) within 24 h. Moreover, if drug treatment is needed, IV antihypertensive agents (which include nicardipine, hydralazine, labetalol, or esmolol) or short-acting ones are preferred.[15]

In the Enhanced Control of Hypertension and Thrombolysis Stroke Study,[16] intensive BP lowering (<140/90 mmHg) was significantly less likely to suffer intracranial hemorrhages. It also showed that mRS score distribution within 90 days was not different across clusters. There were lesser patients in the intensive cluster as compared to the guideline cluster who had intracranial hemorrhage. The proportion of patients with any severe unfavorable incident was not significantly different among the intensive cluster and the guideline cluster. There was no indication of a relationship between intensive BP lowering and the dose (low vs. standard) with alteplase in terms with primary outcome.[16,17]

Table 1: Summary of the different guidelines in the hypertension management in acute ischemic stroke

Guidelines	Eligible for thrombolysis	Not eligible for thrombolysis	Other compelling indication
2018 Guidelines for the early management of patients with acute ischemic stroke (ACC/AHA)	BP must be carefully decreased to SBP of <185 mmHg and DBP of <110 mmHg before giving IV fibrinolysis Until new data will be at hand, in patients eligible for intra-arterial therapy is planned without IV thrombolysis, it is acceptable to maintain BP ≤185/110 mmHg before the procedure	Patients with BP <220/120 mmHg who was not given IV alteplase or EVT without any disease needing acute BP lowering medications, starting or restarting medication within the first 48–72 h post-ictus is not successful to prevent death or dependency Patients with BP ≥220/120 mmHg who was not given IV alteplase or EVT, without disease needing acute BP lowering treatment, the advantage of starting or restarting medications for hypertension within the first 48–72 h is unknown. However, it might be acceptable to decrease BP by 15% within the first 24 h post-ictus	
2018 Canadian stroke best practice recommendations for acute stroke management	The blood pressure needed to attain and maintain in the hyperacute phase is uncertain as of the moment Patients who are for thrombolysis: BP >185/110 mmHg must be managed together with thrombolysis to decrease the possibility of hemorrhagic conversion. Blood pressure must be decreased and maintained <185/110 before giving alteplase and to <180/105 mmHg for the next 24 h post-thrombolysis.	Management of hypertension in patients with acute ischemic stroke or TIA should not be routinely managed	SBP >220 mmHg or DBP >120 mmHg must be managed to lower down the blood pressure around 15%, but not >25%, within the first 24 h. After which, further slow reduction to targets for long-term secondary stroke prevention
2018 ESC/ESH Guidelines for the management of arterial hypertension	BP must be cautiously decreased and sustained at <180/105 mmHg for at least 24 h post-thrombolysis	BP can be reduced by 15% based on clinical judgment within the first 24 h post-ictus	

TIA: Transient ischemic attack, ACC: American College of Cardiology, AHA: American Heart Association, ESC: European Society of Cardiology, ESH: European Society of Hypertension, BP: Blood pressure, DBP: Diastolic blood pressure, IV: Intravenous, SBP: Systolic blood pressure

BP Management in Acute Hypertensive ICH

In patients with spontaneous ICH, elevated BP is common in the acute setting due to several factors which include the following: Stress, pain, elevated intracranial pressure, and history of an acute or continuous increase in BP. It is related with bigger hematoma enlargement, neurological worsening, and death and dependency after ICH.[14] In contrast with AIS, in which consistent U- or J-shaped associations between SBP nadir of 140 and 150 mm Hg and poor outcome have been shown, only 1 study of ICH has shown a poor outcome at low SBP levels (<140 mm Hg).[18] Both the Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH1) trial[19] and the pilot phase Intensive BP Reduction in Acute cerebral hemorrhage trial (INTERACT1)[20] showed lowering of SBP to <140 mmHg to be safe. The INTERACT2 trial did not demonstrate a rise in death or severe adverse outcomes in early aggressive BP lowering.[21]

The INTERACT2 is one of the biggest randomized clinical trials in the ability of intensive BP reduction, in which ICH patients (6 h post-ictus) with SBP between 150 and 220 mmHg (52.0% intensive treatment group with SBP target of <140 mmHg and 55.6% in the standard treatment group SBP <180 mmHg) with principal result of death or major disability. For the secondary end points, it revealed that there is significantly improved functional recovery based on the mRS and superior physical as well as mental health-related quality of life based on the EQ-5D scale in the intensive group. While this study showed promising treatment effect, there was no strong association between outcome and ICH ictus onset to starting treatment. There was also no substantial influence of intensive BP reduction on hematoma expansion. Furthermore, it was found out that one-third of patients who attained the intended SBP level in 1 h and the other half attained the goal at the 6th h, and majority (75%) only have mild-to-moderate volume (<20 mL) of hematomas.[21]

In the 2017 American College of Cardiology (ACC)/AHA/Guidelines, those with SBP >220 mmHg, it is reasonable to start continuous IV medication infusion with judicious BP monitoring. However, immediate lowering SBP to <140 mmHg in those patients 6 h post-ictus with SBP ranging from 150 to 200 mmHg, it was found out that there is no benefit in terms of reduction of mortality or severe incapacitation and may even be evenly potentially harmful.[22]

In the 2018 ESC/ESH Guidelines for the treatment of hypertension in patients with spontaneous ICH, results from a randomized control trial suggested that immediate lowering of blood pressure (within 6h) to <140/90 mmHg did not show benefit on the primary outcome of disability or death at

3 months, but might decrease hematoma expansion, improve functional outcome, and was generally safe.[14] Another RCT, wherein SBP was immediately decreased (<4.5 h) from an average of 200 mmHg to two different goals (140–170 vs. 110–139 mmHg), revealed that aggressive BP lowering still shows no added advantage on the same primary effect and with additional renal adverse consequences. Therefore, immediately decreasing the BP in ICH is not recommended but with some exception: Acute ICH with SBP ≥220 mmHg, although there is still a paucity of data in this type of patients. Consequently, cautiously decreasing the BP through IV infusion may be started.[14]

In the 6th edition of the SSP Handbook for Stroke Prevention, Treatment, and Rehabilitation in 2014, it is recommended that treating hypertension if SBP >180 mmHg and lowering it to 140 mmHg within 7 days is safe and improves outcome in patients with small to moderate-sized ICH not requiring surgical intervention.[15]

In the recent BP-attained analysis of ATACH 2 trial, the proportions of deterioration within 24 h were considerably greater in patient with reduced and sustained SBP of <140 as well as in reduced SBP (within 2 h) but not maintained group in comparison with the reference. In comparison for those patient without control of BP, there are higher proportions of cardiac-related complications within 7 days among patient with reduction and maintenance of SBP <140.[23]

Discussion

The optimal level of BP that should be maintained in patients with AIS is still not well established.[12] Moreover, no RCTs have focused on the management of low BP in stroke. In a systematic analysis (12 studies), it showed that the chances of death or dependence were the same when using either colloids or crystalloids.[12]

BP management depends on whether a patient is eligible or not for IV thrombolysis as well as the presence of any compelling indication to lower down BP early in the acute setting of stroke. For most cases who are not eligible for IV thrombolysis, there is no hurry to bring down the BP in the first few hours after the ictus.

Accordingly, the ACC/AHA, ESC/ESH, and Canadian guidelines agreed to lower BP to <185/105–110 mmHg if a patient is a candidate for IV thrombolysis. In patients with ≥220/110 mmHg who are not eligible for IV thrombolysis, lowering of BP should be kept to 15–25% reduction during the first 24 h of stroke.

Although the choice of antihypertensive agents used during the acute phase of ischemic stroke is still uncertain, IV antihypertensive agents seem reasonable due to their fast onset of action and can be easily titrated to achieve the goal BP level. These agents include nicardipine, labetalol, and urapidil. After the acute period of ischemic stroke, an oral antihypertensive should be started as a secondary prevention of not only ischemic stroke but also ICH as well. However, the choice of the long-acting oral antihypertensive agents would still depend on several factors such as comorbidities and age. In the ESC/ESH guidelines, a single-pill combination of a renin-angiotensin system blocker plus a calcium channel blocker or thiazide or thiazide-like diuretic is recommended as initial management for the majority of hypertensive patients. In the Canadian hypertension guidelines, for patients with diabetes with cardiovascular disease risk or chronic kidney disease, an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) is considered to be the preferred first-line agents. For patient with coronary artery disease, ACEi or ARB and beta-blockers are recommended as good choices. For patients with past stroke or transient ischemic attack, ACEi and/or thiazide diuretic are recommended.

In patients with ICH, the current evidence is less clear whether early intensive BP lowering is really safe. The more recent analysis of ATACH 2 trial is not congruent with the findings seen in INTERACT2 trial. While there is no decline in death or disability, there are signals of harm as shown by higher rates of neurological deterioration and cardiac-related adverse effects in patients with ICH receiving early intensive BP-lowering treatment.[23]

Conclusion

BP management in the setting of AIS and spontaneous ICH is different from the treatment of other hypertensive situations such as hypertensive urgencies and emergencies as well as in the secondary prevention of stroke. Treatment depends on several factors such as timing, comorbidities, and eligibility for thrombolysis. This review of selected research articles and current guidelines on the management of hypertension in acute stroke setting hopes to improve one's understanding of the uniqueness of BP management of the acute phase compared with the non-acute phase both in ischemic and hemorrhagic strokes.

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Current and Emerging Concept

Clinical Presentation, Diagnosis, and Management of Primary Aldosteronism and Pheochromocytoma

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Abstract

Primary hyperaldosteronism (PA) or Conn's syndrome and pheochromocytoma (Pheo) are functioning tumors of the adrenal glands that can cause secondary hypertension. Bilateral adrenal hyperplasia and aldosterone-producing adrenal tumor are the most common causes of PA. Due to the high circulating aldosterone, hypokalemia results which cause weakness, tingling sensation, muscle spasms, and periods of temporary paralysis. Pheo is a rare adrenomedullary tumor that can synthesize, metabolize, store, and secrete catecholamines and their metabolites. A high index of clinical suspicion remains the pivotal point to initiate biochemical studies for Pheo, particularly in those patients with a certain pattern of blood pressure elevation (paroxysmal or alternating with hypotension), drug-resistant hypertension, sudden palpitations (in some patients accompanied by pallor), unexplained sweating, especially during night or in cold weather, and unexplained hyperglycemia. Only after PA and Pheo are biochemically established should imaging be performed. The current imaging modalities include anatomical (computed tomography [CT] and magnetic resonance imaging [MRI]) and functional (molecular) imaging procedures using various radiopharmaceuticals depending on the clinical situation. For equivocal imaging results in PA, bilateral adrenal venous sampling is the "gold standard" to distinguish unilateral from bilateral lesions. Prompt diagnosis is important because delay in the diagnosis and treatment can lead to untoward cardiovascular complications including myocardial infarction, strokes, and fatal arrhythmias. Clinicians must be trained to have the "clinical eye" and awareness of early detection and management of these two curable causes of secondary hypertension.

Key words: Conn's syndrome, pheochromocytoma, primary aldosteronism, resistant hypertension, secondary hypertension

Introduction

Primary hyperaldosteronism (PA) or Conn's syndrome and pheochromocytoma (Pheo) are functioning tumors from the adrenal glands that can cause secondary hypertension.[1,2]

Conn's syndrome is the excess production of the hormone aldosterone from the zona glomerulosa of the adrenal glands. The prevalence of PA has been reported to range from 4.6 to 9.5% among hypertensive individuals.[3,4] The high circulating aldosterone results in hypokalemia which leads to weakness, tingling, muscle spasms, and periods of temporary paralysis.[4,5] Bilateral adrenal hyperplasia and aldosterone-producing adrenal tumor are the most common causes of PA.[6]

Pheochromocytoma (Pheo) is a rare adrenomedullary tumor with an incidence of 0.1–0.6%.[1,7] About 0.05–0.1% of Pheo cases are undiagnosed in autopsy studies.[8] These tumors can synthesize, metabolize, store, and secrete catecholamines and their metabolites.[9] Pheos originate from adrenomedullary chromaffin cells that commonly produce epinephrine, norepinephrine, and dopamine. Chromaffin cells evolve into 80–85% Pheos and 15–20% are paragangliomas.[10]

A high index of clinical suspicion remains the pivotal point to initiate biochemical studies, particularly in those patients with a certain pattern of spells, blood pressure elevation (paroxysmal or alternating with hypotension), drug-resistant hypertension,

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sudden palpitations (in some patients accompanied by pallor), unexplained sweating, especially during night or in cold weather, unexplained hyperglycemia, and a hereditary predisposition for Pheo.[11]

Because PA and Pheo are caused by excess secretion of hormones from functional adrenal tumors, they are also called adrenal hypertension.

Only after PA and Pheo are biochemically proven, imaging should be performed.[6,10] The current imaging modalities include anatomical (CT and MRI) and functional (molecular) imaging procedures using various radiopharmaceuticals depending on the clinical situation. For equivocal imaging results, bilateral adrenal venous sampling is the "gold standard" to distinguish unilateral from bilateral lesions in PA.[6]

Although biochemical testing for PA and Pheo is indicated for symptomatic patients, it is also indicated for patients with incidentally found adrenal lesions. Silent PA and Pheo occur in 2.5–6% and 7–11% of adrenal tumors, respectively.[12]

Moreover, there are identified genetic predispositions or syndromic presentation pointing toward a high likelihood to develop PA and Pheo. In PA, these are patients with familial hyperaldosteronism type I, II, and III, KCNJ5 gene, CACNA1D gene, and multiple endocrine neoplasia type 1.[6] In Pheo, these are patients with von Hippel-Lindau syndrome (VHL), neurofibromatosis type 1 (NF1), mutations of the succinate dehydrogenase genes (SDHB, SDHD), multiple endocrine neoplasia type 2 (MEN2), and hypoxia-induced factor 2A (HIF2A)-related Pheo-polycythemia syndrome.[13,14]

Delay in the diagnosis and treatment leads to untoward cardiovascular (CV) complications, namely myocardial infarction, strokes, fatal arrhythmias, chronic kidney disease, and death, compared with age-, sex-, and blood pressure (BP)-matched essential hypertensives among PA patients.[15] In Pheo, fatal tachyarrhythmia, myocardial infarction, stroke or death, and impaired myocardial function persisting even after normalization of catecholamine levels postoperatively have been reported.[16] Recently, systemic hormonal unloading for PA and PHEO has demonstrated to be beneficial as far as improvement in the CV function and quality of life is concerned.[16-19]

Clinicians must be trained to have the "clinical eye" and awareness of early detection and management of these two (PA and Pheo) curable causes of secondary hypertension to have significant lowering of morbidity and mortality. This is the objective of this concise review.

Clinical Presentations

Silent PA and Pheo or incidentally found tumors occur in 2.5–6% and 7–11% of adrenal tumors, respectively, in both clinical and surgical studies.[11]

Primary Aldosteronism

The clinical picture of PA (hypertension and hypokalemia) is attributed primarily to a resultant hypokalemia due to heightened mineralocorticoid effect of the excessive secreted aldosterone with water reabsorption and potassium urinary excretion in exchange of sodium. On top of high blood pressure, patients complain of weakness, tingling sensation, numbness, difficulty in doing activities such as putting on shirts, climbing up the stairs or getting in or off a vehicle, and even frank paralysis that often becomes the reason for emergency consult or admission.[3-6] Others have been reported to present already with CV complications such as stroke, severe arrhythmia, coronary heart disease, and myocardial infarction.[15] As reported by Mosso, hypertension can be mild (2%), moderate (8%), or severe (13%), among PA patients with hypertension.[20]

Pheochromocytoma

Symptoms associated with Pheo are often misinterpreted due to their similarities to other multisystem disease entities. Patients most commonly present with episodic attacks of elevated blood pressure, pallor, profuse diaphoresis, and palpitations.[11] Soltani *et al*. recently demonstrated that when considering a possible Pheo diagnosis, a clinical symptomatology likelihood ratio of headache, diaphoresis, and palpitations is shown to be significant.[21]

A specific catecholamine-receptor interaction characterizes the clinical picture of Pheo. Smooth muscles stimulation of α2-adrenergic receptors will result in arterial vasodilation and coronary vasoconstriction, and in Pheo, this typical manifestation may include diaphoresis and orthostatic hypotension. Stimulation of β1-adrenergic receptors has a positive chronotropic and inotropic effect in the heart. This, together with the increased release of renin, can contribute to hypertension, palpitations, and tachycardia. Stimulation of β2-adrenergic receptors will induce vasodilation of muscular arteries and some common effects in Pheo include constipation and nausea. β3-adrenergic receptors in adipocytes induce lipolysis and can cause weight loss.[22] Recently, literature have been showing case reports of young individuals in their 20s, unsuspected to have Pheo, presenting with premature CV events, with one succumbing to heart failure. Interestingly, CV anatomic and functional abnormalities reverse after adrenalectomy.[11,22-24]

Diagnostic Approaches

Biochemical Testing

Hypertension and hypokalemia are clinical presentations that lead to investigate patients for PA.[6] Hypokalemia is present only in 9%–37% severe cases of PA. Half of the patients with PA and 17% of those with idiopathic hyperaldosteronism (IHA) had serum potassium concentrations of <3.5 mmol/L in a large single study. The absence of low potassium has a low negative predictive value for the diagnosis of PA and the presence of hypokalemia has low sensitivity.[6]

The sustained elevated circulating aldosterone due to autonomous adrenal lesions suppresses the renin-angiotensin system. The most reliable means available test for screening for

PA is the aldosterone-renin ratio (ARR) with a value of >20. No need for further confirmatory testing, if there is spontaneous hypokalemia, and there is plasma renin below detection levels plus plasma aldosterone concentration (PAC) of >20 ng/dL (550 pmol/L).[6]

In equivocal CT/MRI findings, adrenal venous sampling with cosyntropin stimulation is performed. To confirm successful catheterization, the ratio of cortisol concentrations from the adrenal veins and peripheral veins is utilized. The ratio of more than 5:1 with the continuous cosyntropin infusion protocol and more than 2:1 without cosyntropin use signifies good catheterization.[6,25]

Genetic testing is advised in patients with diagnosis of PA at a younger age (earlier than 20 years) and in those who have a family history of PA or stroke at age <40 years and younger, and for familial hyperaldosteronism type 1 (FH-I) (glucocorticoid remediable aldosteronism [GRA]). Testing for germline mutations in KCNJ5 causing familial hyperaldosteronism type 3 (FH-III) must be conducted on patients with same age groups.[6]

The characteristic clinical features of Pheo signals need for biochemical testing, especially if severe hypertension is occurring in the young. Plasma free or urinary fractionated metanephrine determinations are preferred for the diagnosis of Pheo.[10] In general, it is preferred that specific institutions must develop their own reference values. Plasma metanephrine, but not normetanephrine, was higher in men but reference interval did not differ. A 3-fold increase from the reference intervals from the package inserts of commercial kits is usually utilized to interpret biochemical results. Medications can mildly to markedly raised values for biochemical test results and, therefore, must be stopped 2 to 4 weeks before testing. These are acetaminophen, mesalamine, sulfasalazine, and tricyclic antidepressants.[9-11] Dietary restrictions for a tyramine-rich diet (cheese, nuts, cereal, beer, and wine) are made mainly for the measurement of 3-methoxytyramine, a dopamine metabolite, and blood sample must be collected after an overnight fast. Stabilization of comorbidities is imperative to avoid false low (renal failure) or inadvertently high values (decompensated heart failure, stroke, and obstructive sleep apnea). Plasma metanephrine has shown to be least affected by these conditions.[9,11]

Global metabolite profiling, or simply metabolomics, is a new technology of functional genomics used for investigating metabolite changes associated with some gene mutations. Recently, a new technique, the so-called 1H high-resolution magic angle spinning (HRMAS) nuclear magnetic resonance (NMR) spectroscopy has been employed with the advantages suited for a small sample of tissues.[13,26]

Pheo can be part of several syndromic entities with genetic mutations such as VHL, neurofibromatosis type 1 (NF1), mutations of the succinate dehydrogenase genes (SDHB, SDHD), MEN2, and HIF2A-related PHEO-polycythemia syndrome.[13,14] Genotype-phenotype correlations have recently been shown, including a high risk of metastatic disease development, and therefore, Pheo patients presenting with such must be tested.[10]

Imaging Modalities

In patients with suspected secondary hypertension, such as PA and Pheo, a positive biochemical workup must be shown before any imaging procedures are initiated.[6,10]

In PA, adrenal computed tomography (CT) is the initial imaging tool to look for possible adrenocortical adenoma and to provide landscape for radiologists and surgeons.[6] For small PAs, bilateral nodularity or normal-appearing adrenals interpretation must be done with ample caution. For detecting unilateral aldosterone, excess adrenal venous sampling yields better sensitivity and specificity (95% and 100%, respectively) compared with adrenal CT (78% and 75%, respectively)[6,25] MRI aside from being expensive has less spatial resolution than CT.[6]

Functional imaging procedures have been utilized to assess lateralization of actively secreting tumors.[27] Since its introduction in the 70s, an improved iodocholesterol scintigraphy agent, (6b-131I) iodomethyl-19-norcholesterol (NP-59), has demonstrated significant correlation of function with anatomical abnormalities, although the size of the adenoma affects its finding.[6] It is not reliable if tumor mass is 1.5 cm in diameter and rarely plays a role in subtype evaluation.[6,11] C-Metomidate positron emission tomography (PET)- CT is a good alternative to AVS in the management of PA with a reported specificity of 87% and sensitivity of 76%.[28]

Anatomic imaging with the use of CT has been the preferred initial procedure for localization of Pheos due to its high sensitivity of 90%.[10,29] However, its limitation has been observed in extra-adrenal, recurrent, and metastatic lesions. MRI, on the other hand, is more advantageous in detecting extra-adrenal lesions and is indicated in those with an allergy to contrast, pregnant, or pediatric patients, and those whose contrast medium is a contraindication.[16] Ultrasound sensitivity is poor but very useful in the detection of liver metastasis and lesions in the urinary bladder.[30]

As summarized by Mercado-Asis *et al.*, functional imaging offers the advantage of higher specificity in detecting multifocal and metastatic tumors and can characterize tumoral metabolic activity. I- or (131) I-metaiodobenzylguanidine (MIBG) scintigraphy has the structure similar to NE so it can enter cells through NE transporters. 123I-MIBG is more sensitive and has better detection rate.[11] On the other hand, single-photon emission computed chromatography has been used with CT/MRI for colocalization. MIBG is reserved for volume determination before 131IMIBG therapy for metastatic Pheo.[31]

PET is showing superiority in spatial resolution. 18F-fluorodeoxyglucose PET is the preferred procedure for malignant tumors, especially SDHB-related PHEO since cancer cells readily take up glucose. 18F-fluorodopamine (FDOPA) is a more specific tracer since its structure is similar to dopamine, a catecholamine precursor, and, therefore, enters the cell through NE transporter. This imaging modality has high sensitivity for metastatic tumors.[32] Newer PET scanning tracers have been developed and showed promising results in detection of metastasis and characterization of metabolic activity of

the tumor cells, namely the DOTA peptides – DOTATATE, DOTATOC, and DOTANOC (65). Ga-DOTATOC PET/CT was found superior to FDOPA PET/CT in the diagnosis of metastatic tumors.[11,13]

Management

The control of hypertension and the removal of the adrenal lesion by unilateral adrenalectomy are the mainstay of the treatment for PA and Pheo.

Before patients with PA undergo surgery, both hypertension and hypokalemia should be well-controlled. Caution should be exercised in doing pre-operative barium enema in patients with PA since this may lead to another hypokalemic episode. The mineralocorticoid antagonist (MRA) spironolactone and potassium supplementation go together in the medical treatment of hypokalemia. Potassium supplementation must be withdrawn on post-operative day 1, together with the discontinuation of spironolactone, and reduction of antihypertensive therapy, if appropriate, to monitor success of surgical treatment.[6] To partially suppress pituitary adrenocorticotropic hormone (ACTH) secretion, glucocorticoid-remediable aldosteronism (GRA) should be managed with a glucocorticoid. The starting dose of prednisone is 2.5–5 mg/day whereas that of dexamethasone in adults is 0.125–0.25 mg/day. The glucocorticoid should be taken at bedtime to suppress the early morning ACTH surge.[6] Eplerenone, a selective MRA without antiandrogen and progesterone agonist effects,[33] *in vivo* has 50% of the MRA potency of spironolactone. It is well tolerated although known to be expensive.[6]

CV evaluation is an essential part of pre-operative management in Pheo because they are known to have compromised cardiac function such as subclinical left ventricular failure.[10] Appropriate medical management to decrease the left ventricular function may reduce the perioperative CV complications. For achieving effective α-blockade, both phenoxybenzamine and doxazosin, two α-adrenoceptor antagonists, are preferred[10] with broader experience with the non-competitive α-adrenoceptor blocker phenoxybenzamine. To achieve a stabile situation, 10–14 days of pharmacological pretreatment are advised. Calcium channel blockers have been found to be effective as monotherapy or in combination with α-adrenoceptor blockade.[10]

The posterior retroperitoneal approach with minimal invasive laparoscopic tumor resection is currently the standard approach of surgical management with Pheo.[10] For long-term outcome of operated patients, it is essential to have optimum follow-up for three reasons: (1) To see completion of surgery; (2) tumor recurrence; or (3) development of metastases, even after many years. To date, no pathologic criteria have been established to evaluate tumor benignity or malignancy nor preponderance for metastasis.[10,34] Biochemical evaluation with measurement of plasma or urine metanephrines at 2 to 6 weeks after surgery is recommended to ascertain success of operation. Since there is a risk of local or metastatic recurrences or development of new tumor in 5% of operated Pheo patients during 5-year follow-up, it is recommended to maintain postsurgical follow-up in all operated patients for at least 10 years. Lifelong follow-up is recommended to Pheo patients who are young, those with an extra-adrenal or large tumor, and those who with a germline mutation since they have a high tendency to recur.[10] Inhibition or alteration of certain metabolic processes involved in tumorigenesis is a very promising therapeutic approach.[13,35]

Summary and Clinical Insight

Primary aldosteronism and pheochromocytoma are two common causes of secondary hypertension. Clinicians must have a high index of suspicion when confronted with difficult to treat or resistant types of hypertension, presenting with the symptoms associated with the two. A good "clinical eye" and increased awareness of their pathognomonic clinical presentations may help in the early detection and management of these two causes of adrenal hypertension. Early diagnosis and timely treatment are imperative to prevent long-term hypertension-mediated organ damage and irreversible complications on the cardiocerebrovascular and renal systems, thereby decreasing morbidity and mortality associated with primary aldosteronism and pheochromocytoma.

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