

An Overview of Hypertension Management in different patients' category in the Primary Health Care Centre

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Received: 03 August 2020 / Received in revised form: 14 November 2020, Accepted: 22 November 2020, Published online: 28 November 2020
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Abstract

Background: Hypertension is defined as elevated blood pressure more than 139/89. There is plenty of consideration that must be taken to account when diagnosing hypertension and starting treatment. Hypertension is a well-recognized risk factor for the majority of morbidities, such as cardiovascular, cerebrovascular, and peripheral arterial diseases, as well as mortality. For this reason, the blood pressure must be optimized, under control, and continuously monitored. **Objective:** This literature review aims to target the hypertension treatment for a specific population, such as patients with old age, diabetes, chronic kidney disease, ischemic heart disease, and heart failure. Those populations are at increased risk of developing complications related to uncontrolled hypertension. **Methods:** We searched for relevant articles in the PubMed database using two Mesh terms: "hypertension" and "Management." **Conclusion:** Hypertension is one of the most

prevalent diseases worldwide, and it is positively associated with all-cause morbidities and mortality. Therefore, an intensive program for education, screening, prevention, and treatment is strongly needed in our society; this would help early detection and management before complications emerged. Finally, hypertension has no specific agent to treat; it depends on lifestyle modification, patient character, compliance, cost, and concomitant comorbidities.

Keywords: Hypertension, Diagnosis, Management

Introduction

The prevalence of hypertension (HTN) is kept growing worldwide from 600 million cases in 1980 to 1 billion in 2008 (Kjeldsen et al., 2014; Abd Elwahaab et al., 2019; Yusransyah et al., 2019; Alzahrani et al., 2019). It is also the commonest chronic disease in the United States, affecting more than 45% of adults and remaining the most frequent diagnosis made in primary health care visits (Milani et al., 2020). Despite that HTN is considerably asymptomatic, it is one of the main risk factors for cardiovascular disease (CVD) and mortality (Kjeldsen et al., 2014; Aronow, 2020). It accounts for almost 45% of heart disease-related mortality and 51% of stroke-related mortality (Kjeldsen et al., 2014). Complications of HTN might lead to 9.4 million deaths yearly, and the World Health Organization (WHO) has forecasted this number to be increasing (Kjeldsen et al., 2014). It has been thought that by 2030 approximately a quarter of all deaths globally will be due to CVD (Kjeldsen et al., 2014). Hypertension was found in 69% of patients with first myocardial infarction, 77% of first stroke patients, in 74% of heart failure patients, and 60% of older patients with the peripheral arterial disease (Aronow, 2020). Nevertheless, a significant reduction in death percentage could be seen if HTN is perfectly controlled; For example, it has been predicted in the UK that stroke incidence will be decreased by 28-44% and ischemic heart disease by 20-35% if HTN is well controlled (Kjeldsen et al., 2014).

Initiation of HTN therapy is mainly based on blood pressure readings obtained in the clinic, and all guidelines used a common definition of stage 1 HTN as measured SPB/diastolic (DBP) >139/89 mmHg and stage 2 HTN as >159/99 mmHg (Kjeldsen et al., 2014; Milani et al., 2020). But, blood pressure measurements in the clinic do not precisely capture the average fluctuations in

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blood pressure over days and months (Milani et al., 2020). Several studies have shown that the variability of systolic blood pressure (SPB) is a better predictor of all-cause and cardiovascular disease mortality, stroke, and total cardiovascular disease, in comparison to average SPB (Milani et al., 2020). Therefore, a digital hypertension program is preferred at patients' homes to provide real-time assessment and intervention, leading to a significant reduction in both blood pressure variability and average blood pressure compared to clinic-based care (Milani et al., 2020).

Hypertension Diagnosis and Monitoring

Except for the American Heart Association (AHA), American College of Cardiology (ACC), the Center for Disease Control and Prevention (CDC), and the US Joint National Committee (JNC-8) guidelines discuss the ambulatory or home blood pressure monitoring (ABPM/HBPM) as a tool for diagnosing or monitoring blood pressure (Kjeldsen et al., 2014). Although there is an agreement that a diagnosis of hypertension should be based on multiple clinic BP readings within at least two separate visits, one-four weeks apart, the Canadian Hypertension Educating Program (CHEP) guidelines are more strict (Milani et al., 2020). They recommend that if SBP is 140-160 mmHg or DBP 90-100 mmHg, then clinic BP must be measured on 4-5 separate visits, or self-monitoring/ABPM should be used before establishing the diagnosis of hypertension (Kjeldsen et al., 2014). Hypertension definition has been changed recently by the 2017 ACC/AHA guidelines, from a BP threshold of 140/90 to 130/80 mmHg (Gijón-Conde et al., 2019). However, the 2018 European Society of Cardiology/European Society of Hypertension (ESC/ESH) guidelines defines hypertension as a BP threshold of 140/90 mmHg and above (Gijón-Conde et al., 2019). Consequently, hypertension prevalence increased based on the recent adjustment of 2017 ACC/AHA guidelines, and a significant number of people should receive treatment and follow up (Gijón-Conde et al., 2019).

The ABPM/HBPM has been widely used to diagnose and monitor blood pressure readings and should be strongly considered as the best diagnostic tool, and HBPM can be used if ABPM is unavailable (Kjeldsen et al., 2014; Patney et al., 2015). Nevertheless, only CHEP and NICE guidelines approved these methods to diagnose hypertension and start treatment (Kjeldsen et al., 2014). Despite its beneficial use, ABPM is not extensively available due to the high cost (Patney et al., 2015). Moreover, ABPM/HBPM can also detect white-coat hypertension and masked hypertension (Patney et al., 2015; Travieso-Gonzalez et al., 2019). The definition of white-coat hypertension is high blood pressure readings in the clinic but normal in a clinic setting, and masked hypertension is normal BP readings in the clinic and high in out clinic settings (Patney et al., 2015; Travieso-Gonzalez et al., 2019). There is no treatment given to white-coat hypertension, while masked hypertension is managed similarly to essential hypertension (Patney et al., 2015).

Discussion

Hypertension in the Elderly

Target SBP in the guidelines is below 139 and DBP below 89 for the general population; however, some variations exist for some specific groups of patients (Kjeldsen et al., 2014). The US JNC-7 guidelines define hypertension upon BP thresholds of 140/90 mmHg without concomitant diabetes or chronic kidney disease (CKD) (Shimbo et al., 2014). More recently, the 2014 JNC-8 guidelines recommended a higher SBP threshold (150 mmHg) to initiate therapy and treatment goals in adults aged more than 59 (Kjeldsen et al., 2014; Shimbo et al., 2014; Cryer et al., 2016). Subsequently, many older people in the US are excluded for hypertension management (Shimbo et al., 2014). Additionally, except for AHA/ACC/CDC guidelines, the ESH/ESC, ASH/ISH, French, NICE, CHEP, and China guidelines recommended a higher BP threshold of <150/90 mmHg is appropriate in the elderly population (Kjeldsen et al., 2014). However, it is essential to note that the definition of elderly differs between the guidelines: JNC-8 defines elderly as >59 years of age, China as >64 years of age, and the ASH/ISH, French, NICE, CHEP, and ESH/ESC guidelines defined it as >79 years of age (Kjeldsen et al., 2014). Both the Systolic Hypertension in the Elderly Program (SHEP) and the Hypertension in the Very Elderly Trial (HYVET) showed a clear cardiovascular benefit with SBP <149 mmHg compared to higher readings (Patney et al., 2015). The Japanese Trial to Assess Optimal Systolic Blood Pressure (JATOS) and the Valsartan in Elderly Systolic Hypertension (VALISH) trial did not show benefit for SBP <140 mmHg compared with <150 mmHg (Patney et al., 2015).

Pharmacological treatment of HTN in the elderly includes all the major antihypertensive classes: diuretics, angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), beta-blockers, and calcium channel blockers (CCBs) have similar efficacy in adult for reducing the risk of cardiovascular events and stroke (Aronow, 2020). The choice among which class should be used is based individually on efficacy, tolerability, cost, and concomitant comorbidities (Aronow, 2020). **Table 1** showed the current guideline for antihypertension therapy in specific groups of a patient (Aronow, 2020).

Hypertension in patients with diabetes and/or CKD

Hypertension is a decisive, independent risk factor for morbidity and mortality (Patney et al., 2015). It is commonly associated with chronic kidney impairment, and it can be either a cause or an outcome (Patney et al., 2015). Patients with CKD carry a high risk for hypertension-related morbidities, such as cardiovascular disease (Go et al., 2008). Hence, controlling hypertension is an essential factor in patients with CKD. The target BP with comorbidities was not strictly across the guidelines due to a lack of quality evidence (Kjeldsen et al., 2014). Previously, the target BP based on some guidelines (ESH/ESC 2007 and JNC-7) (Patney et al., 2015) in patients with CKD or diabetes was <130/80 mmHg (Kjeldsen et al., 2014; Patney et al., 2015). Recent guidelines do not support this approach due to insufficient evidence-based (Kjeldsen et al., 2014); therefore, JNC-8 is now recommended to target BP as in the general population (<140/90 mmHg) (Cryer et al., 2016). JNC-8 relied on extensive findings on the Action to Control Cardiovascular Risk in Diabetes (ACCORD-BP) trial,

which predominantly addressed SBP in hypertensive patients with diabetes (Cryer et al., 2016). In scope to the DBP, JNC-8 recommended initiating therapy for hypertensive diabetic patients if DBP >90 mmHg and treatment goal of <90 mmHg (Cryer et al., 2016). These recommendations vary from the previous JNC-7 guidelines, which was suggested to initiate antihypertensive therapy if DBP of >80 mmHg (Cryer et al., 2016), but the recent guidelines adjustment based on the outcomes of the Hypertension Optimal Treatment (HOT) and the United Kingdom Prospective Diabetes Study Group (UKPDS) trials (Cryer et al., 2016).

The pharmacological antihypertensive medications have resulted in an additional impact on certain vital organs, apart from controlling BP, such as cardio or renoprotection, or reduces proteinuria (Cryer et al., 2016). JNC-7 recommended antihypertensive in diabetic patients regardless of race, including

diuretics, ACE inhibitors, Beta-blockers, ARBs, and CCBs (Cryer et al., 2016). However, JNC-8 suggested in black populations to start with thiazide diuretics or CCBs as favored initial treatment groups (Cryer et al., 2016). The ESH guidelines recommend starting ACE inhibitors or ARBs in patients with diabetes mellitus (Cryer et al., 2016). Moreover, the ASH-guidelines recommend ACE inhibitors and ARBs as initial pharmacological therapy in diabetes patients; however, they still recommend CCBs and thiazide diuretics in black individuals (Cryer et al., 2016). In hypertension with CKD, irrespectively to the race, proteinuria degree, or the diabetes status, JNC-8 recommends ACEi or ARBs as initial antihypertensive classes (Patney et al., 2015). Although the use of ACEi or ARBs did not afford cardiovascular protection, almost every other guideline supports their benefit to CKD patients (Cryer et al., 2016).

Table 1. Antihypertensive treatment guidelines

HTN plus:	Non-black	Black	+ stable IHD	+ HFrEF	+ CKD
Drug Of Choice	Thiazide (chlorthalidone) or CCBs. Next: Thiazide/CCBs. Next: Thiazide/CCBs plus ACEi/ARBs	Thiazide/CCBs > than ACEi/ARBs. Consider adding mineralocorticoids antagonist* if the fourth drug need (resistant HTN) to be added <u>in black or white people.</u>	BB**/ACEi or ARBs. If a third Rx is needed, then add thiazide (Chlorthalidone) or CCBs.	BB**/ACEi or ARBs OR ARNI/diuretics with aldosterone antagonist. Non-dihydropyridine CCBs is contraindicated	Stage >2 or 1, 2 with albuminuria >300mg/day should receive: ACEi or ARBs. Next: Add thiazide or CCBs.

IHD: Ischemic Heart Disease. **ARNI:** Angiotensin receptor-neprilysin inhibitor
 * **Mineralocorticoids antagonist:** Spironolactone or Eplerenone are used in treatment-resistant-hypertension
 ****BB:** beta-blockers than can be used in IHD: carvedilol, metoprolol succinate, bisoprolol, metoprolol tartrate, nadolol, propranolol, and timolol. *Beta-blockers that can be used in HFrEF: carvedilol, metoprolol succinate, and bisoprolol.

Hypertension in patients with Heart Failure

Hypertension is the most common risk factor for heart failure development (Travieso-Gonzalez et al., 2019). The Framingham Heart Study noticed that heart failure development is 91%, preceded by hypertension in a 20-years follow-up (Travieso-Gonzalez et al., 2019; Slivnick and Lampert, 2019). The first typical manifestation of hypertension on the heart structures is left ventricular diastolic dysfunction (Travieso-Gonzalez et al., 2019; Sorrentino, 2019). The chronic overload pressure is the leading cause of left ventricular hypertrophy (LVH), and eventually, the condition will progress to involve the systolic function by the chronic volume and pressure overload (Sorrentino, 2019). If left untreated, LVH will progress to diastolic dysfunction, and the patient starts to be symptomatic; this condition is known as heart failure with preserved ejection fraction (HFpEF) (Sorrentino, 2019). At this phase, abnormalities in myocyte relaxation and progressive extracellular fibrosis lead to ventricular filling impairment (Sorrentino, 2019). Ultimately, a large group of patients with longstanding hypertension progresses to develop systolic dysfunction and clinical heart failure with reduced ejection fraction (HFrEF) (Slivnick and Lampert, 2019; Sorrentino, 2019). Hypertension is one of the major modifiable risk factors in HFpEF evolution and progression (Slivnick and Lampert, 2019). Treatment of HTN has been shown to prevent the progression of HF in many clinical trials, especially among older adults (Slivnick

and Lampert, 2019). Furthermore, reduction in HF incidence among postmenopausal women is markedly associated with a healthy lifestyle, including a high-quality diet, improved physical exercise, maintain healthy body weight, and no tobacco use (Slivnick and Lampert, 2019; Tam et al., 2017). These factors are considered effective similarly to the non-pharmacological treatment options for HTN (Slivnick and Lampert, 2019).

The primary prevention of hypertensive heart failure is the most effective method before pathological remodeling occurs (Sorrentino, 2019). Treatment of hypertension has been resulted in reducing LVH and further consequences (Sorrentino, 2019). Several studies have shown that specific agents can demonstrate LVH regression, such as CCBs, diuretics, and beta-blockers (Slivnick and Lampert, 2019). Furthermore, agents targeting the renin-angiotensin-aldosterone system (RAAS) led to higher rates of LVH reversal (Slivnick and Lampert, 2019). Optimally, ACEi, ARBs, dihydropyridine CCBs, and thiazide diuretics are considered the most effective heart failure agents compared to alpha or beta-blockers (Sorrentino, 2019). These agents are in match with the current hypertension treatment guidelines (Sorrentino, 2019). The preferred option for preventing hypertensive heart failure is thiazide, followed by ACEi/ARBs (Sorrentino, 2019). Hydralazine or long-acting nitrates should be optioned in African Americans with NYHA class III-IV heart failure already on ACEi/ARBs, beta-blockers, and

mineralocorticoid antagonists (Sorrentino, 2019). A recently published PARADIGM-HF trial showed angiotensin-neprilysin inhibitors (ARNI) to effectively reduce mortality in patients with HFrEF and NYHA class II-III symptoms despite using the above agents (Sorrentino, 2019). Blood pressure must meet the target based on ACC/AHA and JNC-8 guidelines (Sorrentino, 2019). Non-pharmacological treatment for hypertensive heart failure includes dietary and lifestyle modification (Slivnick and Lampert, 2019; Agha et al., 2014). Blood pressure salt sensitivity plays a significant role in heart failure development and progression (Elijovich et al., 2016). Moreover, aerobic exercise is not only recommended for controlling HTN but also in heart failure after showing clear benefits in a recent randomized trial (Kitzman et al., 2016).

Conclusion

Elevated blood pressure is one of the most prevalent comorbidities worldwide, and the incidence is increasing to exceed 1 billion people nowadays. Hypertension is generally asymptomatic, but it is a major risk factor for cardiovascular disease, cerebrovascular events, and overall mortality. Elevated blood pressure is a difficult diagnosis to be established since BP is variable throughout the day. A newly approved but not widely used hypertension diagnosis method: ambulatory blood pressure monitoring or home blood pressure monitoring. These methods are preferred to discover the precise time of elevated BP and also rule out white-coat hypertension. Furthermore, it is quite challenging when to initiate medical therapy for high BP values, in the presence of different guidelines. Starting drug therapy for high BP readings must be followed by guidelines and physician clinical judgment. There is no best medication for hypertension; it depends on specific patient characteristics and criteria. Those include the patient's age, sex, gender, presence of comorbidities, tolerability, and cost. By controlling blood pressure under optimal values, multiple consequences can be avoided, and the overall quality of life will be increased. Furthermore, hypertension screening is not widely performed, and we recommend awareness symposiums or TV programs to encourage people to screen and monitor their blood pressure.

References

- Abd Elwahaab, H. A., Rahmy, A. F., Hagag, A. A., Fares, H. M., & Fouad, S. A. (2019). Effect of Aerobic exercises on Blood coagulation and Fibrinolysis factors in Elderly Hypertensive patients. *J Adv Pharm Edu Res*, *9*(1), 44-48.
- Agha, G., Loucks, E. B., Tinker, L. F., Waring, M. E., Michaud, D. S., Foraker, R. E., ... & Eaton, C. B. (2014). Healthy lifestyle and decreasing risk of heart failure in women: the Women's Health Initiative observational study. *Journal of the American College of Cardiology*, *64*(17), 1777-1785. doi: 10.1016/j.jacc.2014.07.981. Epub 2014 Oct 21. PMID: 25443698; PMCID: PMC4254927.
- Alzahrani, S., Alosaimi, M. E., Alamri, A. A., Alotaibi, M., Almatar, E. A., Almanea, B. A., ... & Al-Shams, A. A. (2019). Association between Knowledge and Drug Adherence in Patients with Hypertension in Saudi Arabia. *Archives of Pharmacy Practice*, *10*(3), 71-76.
- Aronow, W. S. (2020). Managing the elderly patient with hypertension: current strategies, challenges, and considerations. *Expert Review of Cardiovascular Therapy*, *18*(2), 117-125. doi: 10.1080/14779072.2020.1732206. Epub 2020 Feb 23. PMID: 32066287.
- Cryer, M. J., Horani, T., & DiPette, D. J. (2016). Diabetes and hypertension: a comparative review of current guidelines. *The Journal of Clinical Hypertension*, *18*(2), 95-100. doi: 10.1111/jch.12638. Epub 2015 Aug 3. PMID: 26234374.
- Elijovich, F., Weinberger, M. H., Anderson, C. A., Appel, L. J., Bursztyn, M., Cook, N. R., ... & Laffer, C. L. (2016). Salt sensitivity of blood pressure: a scientific statement from the American Heart Association. *Hypertension*, *68*(3), e7-e46. doi: 10.1161/HYP.000000000000047. Epub 2016 Jul 21. Erratum in: *Hypertension*. 2016 Oct;68(4):e62. PMID: 27443572.
- Gijon-Conde, T., Sanchez-Martinez, M., Graciani, A., Cruz, J. J., Lopez-Garcia, E., Ortola, R., ... & Banegas, J. R. (2019). Impact of the European and American guidelines on hypertension prevalence, treatment, and cardiometabolic goals. *Journal of hypertension*, *37*(7), 1393-1400. doi: 10.1097/HJH.0000000000002065. PMID: 31145710.
- Go, A. S., Chertow, G. M., Fan, D., McCulloch, C. E., & Hsu, C. Y. (2004). Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *New England Journal of Medicine*, *351*(13), 1296-1305. doi: 10.1056/NEJMoa041031. Erratum in: *N Engl J Med*. 2008;18(4):4. PMID: 15385656.
- Kitzman, D. W., Brubaker, P., Morgan, T., Haykowsky, M., Hundley, G., Kraus, W. E., ... & Nicklas, B. J. (2016). Effect of caloric restriction or aerobic exercise training on peak oxygen consumption and quality of life in obese older patients with heart failure with preserved ejection fraction: a randomized clinical trial. *Jama*, *315*(1), 36-46. doi: 10.1001/jama.2015.17346. PMID: 26746456; PMCID: PMC4787295.
- Kjeldsen, S., Feldman, R. D., Lisheng, L., Mourad, J. J., Chiang, C. E., Zhang, W., ... & Williams, B. (2014). Updated national and international hypertension guidelines: a review of current recommendations. *Drugs*, *74*(17), 2033-2051. doi: 10.1007/s40265-014-0306-5. PMID: 25315030; PMCID: PMC4224739.
- Milani, R. V., Wilt, J. K., Milani, A. R., Bober, R. M., Malamud, E., Entwisle, J., & Lavie, C. J. (2020). Digital Management of Hypertension Improves Systolic Blood Pressure Variability. *The American journal of medicine*, *133*(7), e355-e359. doi: 10.1016/j.amjmed.2019.10.043. Epub 2019 Dec 20. PMID: 31870666.
- Patney, V., Whaley-Connell, A., & Bakris, G. (2015). Hypertension management in diabetic kidney disease. *Diabetes Spectrum*, *28*(3), 175-180. doi:10.2337/diaspect.28.3.175
- Shimbo, D., Tanner, R. M., & Muntner, P. (2014). Prevalence and characteristics of systolic blood pressure thresholds in

- individuals 60 years or older. *JAMA internal medicine*, 174(8), 1397-1400. doi: 10.1001/jamainternmed.2014.2492. PMID: 24934716; PMCID: PMC4233656.
- Slivnick, J., & Lampert, B. C. (2019). Hypertension and heart failure. *Heart failure clinics*, 15(4), 531-541. doi: 10.1016/j.hfc.2019.06.007. Epub 2019 Jul 31. PMID: 31472888.
- Sorrentino, M. J. (2019). The evolution from hypertension to heart failure. *Heart failure clinics*, 15(4), 447-453. doi: 10.1016/j.hfc.2019.06.005. Epub 2019 Aug 7. PMID: 31472880.
- Tam, M. C., Lee, R., Cascino, T. M., Konerman, M. C., & Hummel, S. L. (2017). Current perspectives on systemic hypertension in heart failure with preserved ejection fraction. *Current hypertension reports*, 19(2), 12. doi: 10.1007/s11906-017-0709-2. PMID: 28233237; PMCID: PMC5503692.
- Travieso-Gonzalez, A., Núñez-Gil, I. J., Riha, H., Donaire, J. A. G., & Ramakrishna, H. (2019). Management of arterial hypertension: 2018 ACC/AHA versus ESC guidelines and perioperative implications. *Journal of cardiothoracic and vascular anesthesia*, 33(12), 3496-3503. doi: 10.1053/j.jvca.2019.03.068. Epub 2019 Apr 3. PMID: 31078374.
- Travieso-Gonzalez, A., Núñez-Gil, I. J., Riha, H., Donaire, J. A. G., & Ramakrishna, H. (2019). Management of arterial hypertension: 2018 ACC/AHA versus ESC guidelines and perioperative implications. *Journal of cardiothoracic and vascular anesthesia*, 33(12), 3496-3503. doi: 10.1053/j.jvca.2019.03.068. Epub 2019 Apr 3. PMID: 31078374.
- Yusransyah., Halimah, E., & Suwantika. A.A. (2019). Utilization and cost minimization study of antihypertensive drugs in primary healthcare centers. *Journal of advanced Pharmacy education and research*, 9(4), 83-88.