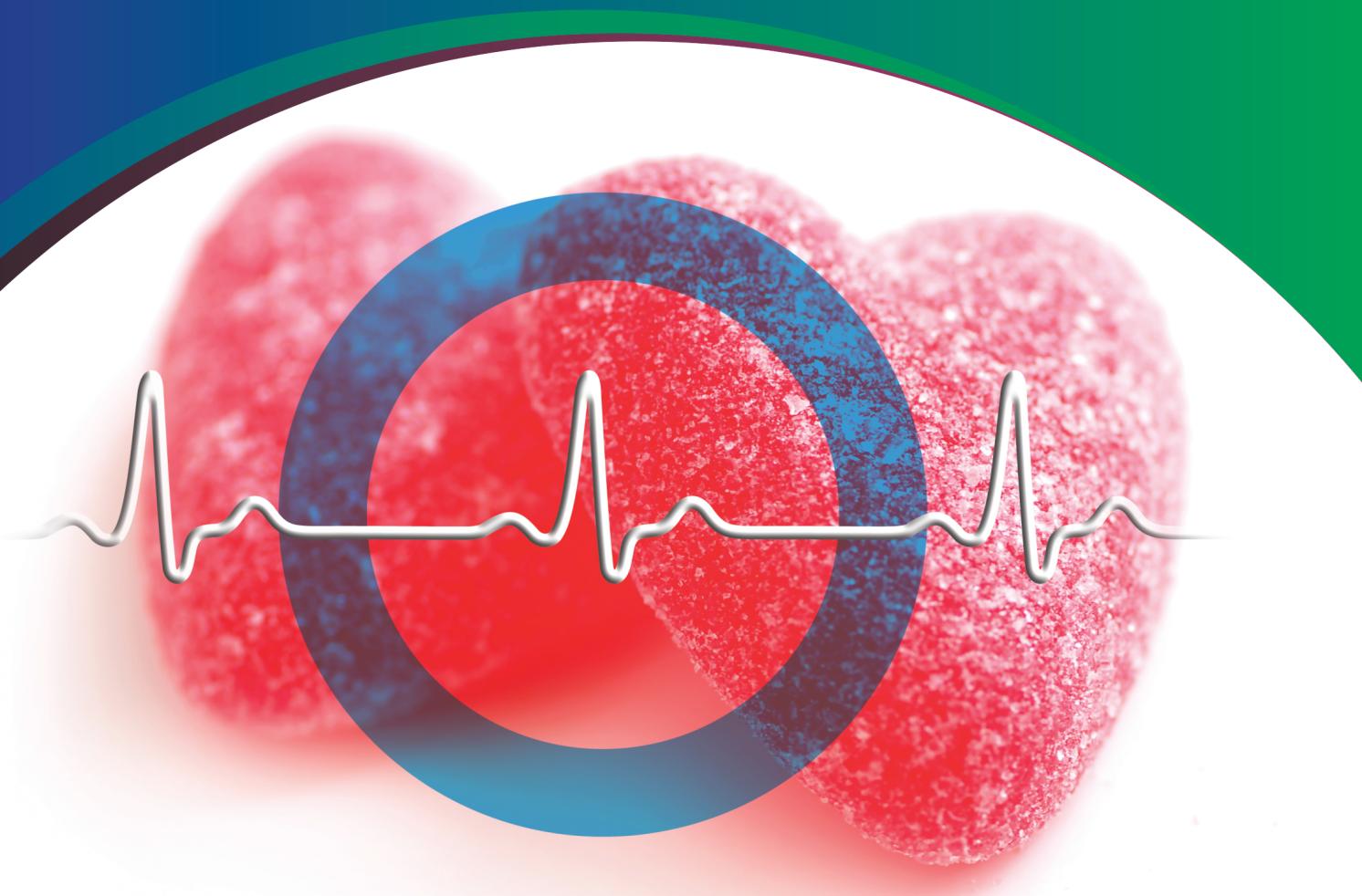


Post Graduate Excellence Program on

CARDIOMETABOLIC CHALLENGES



Course Director

Michael D. Klein, MD

Clinical Professor of Medicine
Boston University School of Medicine,
Boston MA

Module 1

Hypertension

Course code: S.PPCARDIOMET19ml

Program Information

Needs assessment

Hypertension and diabetes are important components of metabolic syndrome, accounting for significant morbidity and mortality worldwide. Both disorders if left untreated can progress to incur widespread end-organ damage, leading to a range of complications. This educational activity provides current updates related to hypertension, diabetes, and their complications; and addresses challenges related to them.

Learning objectives

1. Highlighting the need for end-organ protection in hypertension
2. Current hypertension management approach and indications for combination antihypertensive therapy
3. Highlighting the need for optimal glycemic control for preventing diabetes complications
4. Current recommended diagnostic and management approach for diabetes, with or without comorbidities

Target participants

Physicians and cardiologists

Course Director

Michael D. Klein, MD

Clinical Professor of Medicine

Boston University School of Medicine,

Boston MA

Dr. Klein has nothing to disclose in regards to commercial support.

Method of participation in the program

- Study all parts of the educational activity
- Submit the posttest questions with answers, evaluation and request for certificate of participation forms
- A certificate of participation will be issued by Boston

University School of Medicine upon completing the evaluation and the posttest with a score of 60% or better.

Program activity

Release date: 1st August 2018

Expiration date: 31st July 2019

Course code: S.PPPCARDIOMET19m1

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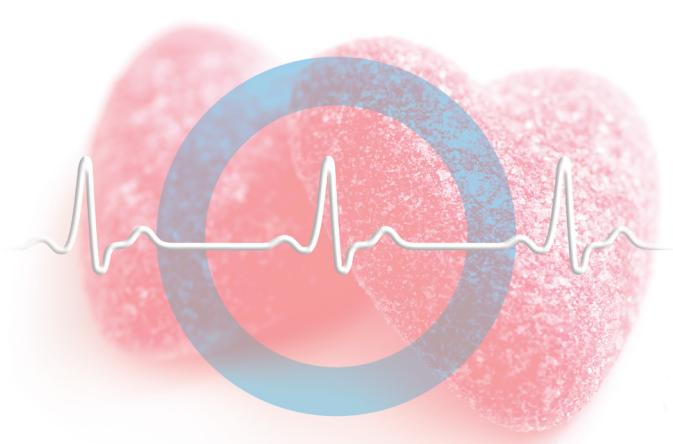
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CONTENTS

SECTION 1

CURRENT UPDATES ON HYPERTENSION AND END-ORGAN DAMAGE

4

SECTION 2

CURRENT UPDATES ON DIAGNOSIS AND MANAGEMENT OF HYPERTENSION

9

AN INTRODUCTION...

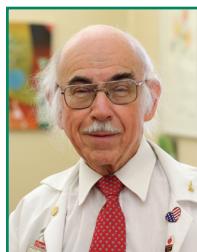
A 60 year old male with known hypertension for 25 years presented to the emergency department with progressive bilateral leg swelling. There was no prior history of diabetes, coronary or peripheral vascular disease. Medications included hydrochlorothiazide 12.5 mg/day and amlodipine 5 mg/day. Pertinent findings on exam included BP 126/98, HR 110, no JVP or HJR, no carotid or femoral bruits, bilateral 2+ leg edema, one half way to the knees, bibasilar rales, no cardiac murmurs, normal heart sounds with a loud LV S₄.

Initial lab data revealed SpO₂ 94%, BUN 48 mg/dl, creatinine 2.8 mg/dl, urinary albumin/creatinine ratio of 150 mg/gm with eGFR of 29 ml/min, sodium 133 mEq/L, potassium 3.2 mEq/L, glucose 100 mg/dl. ECG revealed sinus tachycardia, left atrial enlargement, and left ventricular hypertrophy with strain pattern.

The patient was hospitalized and diuresed to a weight of 70 kg. Repeat lab showed a creatinine of 1.6 mg/dl with an eGFR of 49 ml/min. Repeat Na/K were 136 and 3.6 mEq/L respectively. Telmisartan 20 mg/day was added to his anti-hypertensive regimen.

SECTION 1

Current updates on Hypertension and end-organ damage



Course Director

Michael D. Klein, MD

Clinical Professor of Medicine
Boston University School of Medicine,
Boston MA

OVERVIEW

Hypertension, defined as chronic elevation of systemic arterial pressure, is one of the most common chronic disorders worldwide. It poses significant public health challenge, particularly because of its association with cardiovascular, renal, and cerebrovascular complications.¹ In overwhelming majority of patients (90%), there is no identifiable underlying etiology for hypertension; this condition is labeled as essential hypertension. In contrast, secondary hypertension is usually a result of an underlying and potentially treatable cause such as renal parenchymal disease, aortic coarctation, atherosclerotic renal artery stenosis, Cushing's syndrome, primary hyperaldosteronism, hyperthyroidism, hyperparathyroidism, and obstructive sleep apnea (Table 1).^{1,2} Secondary hypertension should be diagnosed early as it can predispose to both cardiovascular (CV) and renal complications, and is additionally a pre-eminent cause of treatment-resistant hypertension.²

Both the incidence and prevalence of hypertension increases with age. Traditionally, systolic blood pressure (SBP) ≥ 140 mm Hg and diastolic blood pressure (DBP)

Table 1. Important causes of secondary hypertension

- Renal parenchymal disease
- Renal artery stenosis
- Primary aldosteronism
- Pheochromocytoma
- Hypothyroidism
- Hyperthyroidism
- Cushing's syndrome
- Coarctation of aorta
- Medications (NSAIDs, steroids, oral contraceptives)

Sources: Puar TH, Mok Y, Debajyoti R, Khoo J, How CH, Ng AK. Secondary hypertension in adults. *Singapore Med J*. 2016 May;57(5):228-32.

≥ 90 mm Hg were widely accepted as standard cut-offs for initiation of antihypertensive treatment.³ However, the recent American College of Cardiology/American Heart Association (ACC/AHA) guidelines⁴ on high blood pressure in adults have lowered the cut-off range for initiation of antihypertensive treatment. They categorize average SBP between 120-129 mm Hg and average DBP < 80 mm Hg as elevated blood pressure (eliminating previous

category of “prehypertension”); average SBP between 130-139 mm Hg or average DBP between 80-89 mm Hg as stage 1 hypertension; and average SBP \geq 140 mm Hg or average DBP \geq 90 mm Hg as stage 2 hypertension. These guidelines recommend lifestyle changes alone in patients with elevated blood pressure; and lifestyle changes with or without antihypertensive therapy in patients with stage 1 and stage 2 hypertension (see treatment section for details). These recommendations therefore emphasize need to initiate treatment for hypertension at an early stage, thereby effectively stemming both development and progression of hypertension-induced end-organ damage.

Hypertension is a robust predictor of future CV risk and the leading cause of CV deaths worldwide. Although traditionally, importance of therapeutically targeting DBP to optimize CV risk was recognized, recent data indicates otherwise, suggesting that SBP may be potentially more potent risk factor for CV disease compared to DBP.⁵ More specifically, DBP remains a strong driver of coronary risk in young subjects with hypertension; in contrast, SBP appears to be more instrumental in augmenting coronary risk in the elderly.⁶

Hypertension has a complex origin, with potential interplay between genetic and different environmental risk factors eventually leading to its development.¹ Several environmental factors implicated in risk of hypertension have been identified, although individual response to these risk factors can vary depending on genetic susceptibility. Prominent risk factors of hypertension include stress, obesity, reduced physical activity, tobacco smoking, high salt diet, and vitamin D deficiency.^{7,8} Diagnosis of hypertension should be based on the average of at least two office blood pressure readings, preferably taken on two different occasions using either a mercury sphygmomanometer or another non-invasive blood pressure measuring device. Additionally, self-blood pressure monitoring is also regarded as a useful adjunct to office blood pressure measurement, and is therefore deemed crucial for establishing diagnosis of hypertension.⁴ Lifestyle interventions, often with pharmacological therapy (mono- or combination antihypertensive therapy) can facilitate achievement of blood pressure goals, and optimize overall patient outcomes, including their CV risk.¹

BURDEN OF HYPERTENSION: WORLDWIDE AND THE MIDDLE-EAST

Hypertension is widely prevalent across the world. More concerning is the fact that its burden has been steadily

increasing worldwide in the last few years. Although previously thought to predominantly afflict the developed countries, population-based data of the last two decades has shown steady increase in the prevalence of hypertension in the developing countries (both low and middle-income countries) as well, justifying its status as a truly “global” disorder.^{9,10} A systemic analysis of population-based studies recently published in the *Circulation* journal¹⁰ revealed that 1.39 billion adults worldwide had hypertension in 2010, representing 31% of the global adult population. The report also highlighted clear regional disparity in prevalence of hypertension, citing three-times higher prevalence of hypertension in low/middle-income countries compared to high-income countries (1.04 billion vs. 349 million respectively); Figure 1.

Epidemiological data related to prevalence of hypertension in the Middle-East is limited. A systematic review¹¹ of online data published in 2013 revealed high prevalence of hypertension among Arabs (29.5%), much of which was attributed to high prevalence of obesity, physical inactivity, urbanization, industrialization, and increased consumption of processed food with high salt and fat intake. This systematic review also highlighted wide variation in the prevalence of hypertension in different Middle-East countries. More recently, the Prospective Urban Rural Epidemiology (PURE) study¹² evaluated burden of hypertension in 52 urban and 35 rural communities of four Middle-East countries (Iran, Occupied Saudi Arabia, UAE, and Occupied Palestinian Territory). Age-standardized prevalence rate of hypertension in these four countries was shown to be 33%, being higher in the rural than urban dwellers. Importantly, only 49% of hypertensive subjects in this study were aware of their diagnosis. While 47% hypertensive patients received treatment, only 19% of them had their blood pressure optimally controlled. These findings showing high prevalence of hypertension in the Middle-East and poor awareness related to it represents a grim scenario which needs to be addressed at the earliest. Regular screening for high blood pressure in the Middle-East population, and early initiation of antihypertensive management should be instituted as a routine standard of care, thereby stemming development of its end-organ complications early.

PATHOPHYSIOLOGY OF HYPERTENSIVE END-ORGAN DAMAGE

Persistently elevated blood pressure has deleterious effects on several organs of the body. The mechanism, although

FIGURE 1 Prevalence of hypertension in high- and low/middle-income countries



SOURCE: Mills KT, Bundy JD, Kelly TN, Reed JE, Kearney PM, Reynolds K, Chen J, He J. Global Disparities of Hypertension Prevalence and Control: A Systematic Analysis of Population-Based Studies From 90 Countries. *Circulation*. 2016 Aug 9;134(6):441-50.

poorly defined, is multifactorial. It is well-established that chronic, untreated hypertension increases systemic pressure and provokes hemodynamic overload; additionally inducing several molecular and hormonal changes, thereby adversely affecting cardiac, renal, and cerebrovascular functions. A large body of current research indicates that oxidative stress and generation of excess reactive oxygen species (ROS) is an early event in this pathogenetic pathway, leading to pathological changes in the vasculature of different target organs (including heart, brain, and kidneys). Endothelial dysfunction and platelet activation are noteworthy in this regard. Chronically elevated blood pressure additionally promotes prothrombogenic state, impaired fibrinolysis, and increased collagen turnover due to altered concentration of matrix metalloproteinases (MMP), consequently increasing arteriolar thickening, impairing angiogenesis, and adversely affecting both micro- and macrocirculation of the end-organs.^{13,14} In addition, oxidative stress also facilitates expression of several adhesion molecules on the endothelial surface, enhancing influx of inflammatory cells, leading to a predominant proinflammatory state. Inflammatory cells in turn generate ROS, further augmenting oxidative stress. This inflammation-oxidative stress interplay accompanies most hypertensive states, and is also an important contributor to its end-organ complications.¹⁵

RAS is an important contributor to end-organ damage

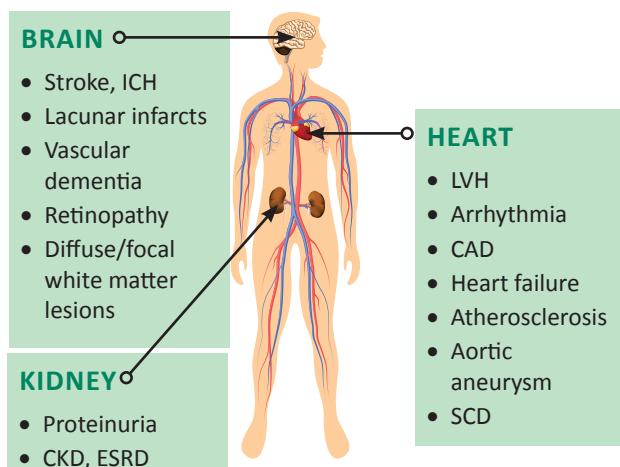
Several lines of evidence suggest a crucial role of renin-angiotensin system (RAS) in the pathogenesis of

hypertensive end-organ damage through mechanisms beyond its blood pressure modulation effect. The role of RAS in neurohormonal regulation and control of blood pressure cannot be overemphasized. RAS is a potent regulator of arterial blood pressure. Angiotensin II, a component of RAS, is a known vasoconstrictor and is additionally involved in renal sodium and water retention. Angiotensin II activation also leads to endothelial dysfunction, increased oxidative stress, and widespread proliferative and fibrotic changes, both pathogenic to the systemic vasculature. These changes promote development of end-organ dysfunction. Therapeutically targeting RAS through RAS blockers not only optimizes blood pressure control, but also provides end-organ protection, independent of blood pressure-lowering effects of these agents.¹⁶

Cardiovascular and cerebrovascular complications in hypertension

Cardiovascular end-organ damage is common in persistent hypertension (Figure 2). It is primarily a result of structural and functional changes in the heart which eventually compromise myocardial function. Among 17 million CV deaths that occur annually worldwide, hypertension alone accounts for 9.4 million deaths. Globally, hypertension is a contributor to 45% deaths due to ischemic heart diseases (IHD) and 51% deaths due to strokes.¹⁷ Majority of hypertensive patients are initially asymptomatic (subclinical coronary artery disease [CAD]), although eventually they can develop several life-threatening CV manifestations including coronary events, heart failure

FIGURE 2 End-organ damage in hypertension



LVH-Left ventricular hypertrophy; CAD-Coronary artery disease; ICH-Intracerebral hemorrhage; ESRD-End-stage renal disease, CKD-Chronic kidney disease; SCD-Sudden cardiac death

Source: Schmieder RE. End Organ Damage In Hypertension. *Dtsch Arztebl Int.* 2010 Dec; 107(49): 866-873.

and arrhythmias. Notable structural and functional CV complications in hypertensive patients include left ventricular hypertrophy (LVH) with concomitant decrease in left ventricle cavity size, reduced cardiac reserve, left ventricular diastolic dysfunction followed by decrease in left ventricular ejection fraction (LVEF), atrial and ventricular arrhythmias. In turn, LVH is a robust risk factor for acute myocardial infarction (AMI), heart failure, and sudden cardiac deaths (SCD). Hypertension is an independent facilitator of atherosclerotic plaque formation. Hemodynamic overload, mechanical stress on arterial wall, and endothelial dysfunction promote atherosclerotic plaque formation and increases plaque vulnerability, thereby increasing risk of coronary events in hypertensive patients.^{18,19} Indeed, atherosclerotic CAD is a common form of CV end-organ damage in hypertension.¹⁹

Elevated blood pressure also adversely affects both cerebral micro- and macrocirculation. Vascular (ischemic) and hemorrhagic strokes are recognized cerebrovascular complications of hypertension. Although ischemic strokes are the most common, cerebral bleeds, lacunar infarcts, focal and/or diffuse cerebral white matter lesions are also notable cerebrovascular complications in hypertensive patients. Vascular dementia is commonly seen in poorly-controlled hypertension.¹⁸

Renal complications in hypertension

Sustained and poorly-controlled high blood pressure

also adversely affects renal vasculature. Chronic kidney disease (CKD) with or without progression to end-stage renal disease (ESRD) is an end-organ manifestation of persistently elevated blood pressure (Figure 2). According to available data, up to 35% patients with hypertension and elevated CV risk have eGFR < 60 mL/min/1.73 m². Also, comorbid CKD considerably worsens prognosis in hypertensive patients with pre-existing CV disease, particularly in those with stable CAD, heart failure, peripheral arterial disease, and coronary interventions.²⁰ Hypertensive patients with comorbid diabetes and preexisting CKD have augmented risk of renal injury. Maximal systolic pressure, nocturnal blood pressure elevations, and blood pressure variability are important determinants of renovascular injury in hypertensive patients.^{18,21}

Hypertension-induced endothelial dysfunction, injury to the podocytes and glomerular basement membrane (GBM) alter filtration capacity of glomerular bed and lead to proteinuria (albuminuria). Renal autoregulatory responses are preserved early in essential hypertension, which prevents direct barotrauma to the glomerulus, and hence significant proteinuria is usually absent early in the disease process.²¹ Nonetheless, as hypertensive state persists, preglomerular capillaries develop ischemic changes (nephrosclerosis) due to which autoregulatory responses are eventually compromised. This predisposes to development of barotrauma-mediated focal segmental glomerulosclerosis, loss of glomerular capillaries, and alteration in their filtration capacity, consequently leading to CKD and its progression to ESRD.^{21,22}

HYPERTENSION AND DIABETES COMORBIDITY

Hypertension frequently coexists with diabetes, significantly increasing complication rates and worsening outcomes in subjects with this comorbidity. More than 50% of patients with diabetes have coexisting hypertension. Comorbid hypertension incurs high risk of both micro- and macrovascular complications in patients with diabetes, particularly aggravating their risk of CV diseases. Patients with diabetes with coassociated hypertension have four-times higher risk of CV diseases, including CAD and stroke, compared to their counterparts with normal blood pressure. Notably, hypertension is an independent predictor of both CV and renal diseases, and further augments risk of these complications in patients with diabetes-hypertension comorbidity.²³ A recently

performed analysis of Framingham data showed that in newly-diagnosed diabetic patients without previous history of CV events, concurrent hypertension at time of diabetes diagnosis increased rates of both all-cause mortality (32 versus 20 per 1000 person-years) and CV events (52 versus 31 per 1000 person-years) compared to non-hypertensive patients. After adjustment of variables, comorbid hypertension lead to 72% increased risk of all-cause deaths and 57% increased risk of any CV events in patients with diabetes.²⁴ Furthermore, when hypertension concurs with pre-existing diabetic kidney disease, it not only increases CV risk, but also hastens progression towards early ESRD.²⁵

Increased frequency with which hypertension and diabetes cooccur has prompted investigators to suspect involvement of common genetic and/or environmental risk factors, along with shared pathogenetic pathway involved in development of this comorbidity. Indeed, insulin resistance, in addition to being a precursor of type 2 diabetes, is also postulated to have a role in hypertension development. Oxidative stress, inflammation, and obesity are other principal drivers of this common pathogenetic metabolic pathway.²⁶ Early and aggressive control of blood pressure in hypertensive patients with diabetes can reduce risk of potentially lethal CV events and renal disease progression, thereby significantly improving overall patient outcomes.^{24,25}

CONCLUSION

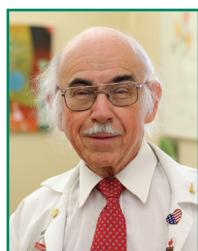
Hypertension is a common CV disorder worldwide which if left untreated can predispose to serious end-organ complications. Essential hypertension is the most common form of hypertension due to an unknown etiology, and affects nearly 90% of hypertensive patients. Hypertension is a major risk factor for several CV diseases and also an independent predictor of renal injury. Risk of these complications is aggravated in patients with hypertension-diabetes comorbidity. Timely detection of hypertension in patients with or without diabetes and its early, aggressive control can significantly reduce CV events and renal disease progression.

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SECTION 2

Current updates on Diagnosis and management of hypertension



Course Director

Michael D. Klein, MD

Clinical Professor of Medicine
Boston University School of Medicine,
Boston MA

DIAGNOSIS AND MANAGEMENT OF HYPERTENSION

The need for accurate and reliable measurement of blood pressure to establish diagnosis of hypertension cannot be overemphasized. Office (clinical) blood pressure recording using mercury sphygmomanometer, for long, was recognized as the “gold standard” method for blood pressure measurement.^{1,2} Aneroid sphygmomanometers were introduced as replacements for mercury devices. They continue to be widely used and provide accurate blood pressure measurements, additionally obviating risk of mercury spills and its toxicity. More recently, digital (automated) blood pressure measurement devices have been introduced as mercury-free alternatives which employ oscillometric technique for blood pressure recording. In a recent study,² aneroid sphygmomanometers showed higher sensitivity and specificity (86.7% and 98.7%) compared to digital devices (80% and 67.7%) for blood pressure measurement. Blood pressure cut-offs at which lifestyle interventions with or without antihypertensive therapy should be initiated; along with treatment goals have been specified in several guidelines, including the JNC 8³ and recent ACC/AHA guidelines.⁴

Hypertension diagnosis should be strictly based on

office blood pressure measurement. Blood pressure measurement should be ideally recorded on at least two occasions; their average readings provides a more reliable estimate of actual blood pressure. Additional need for performing out-of-office blood pressure measurements (ambulatory blood pressure monitoring [ABPM] and home blood pressure monitoring [HBPM]) is now emerging, particularly for ruling out “white coat hypertension” and “masked hypertension” effects in subjects not receiving antihypertensive medications.⁴ In fact, both ABPM and HBPM appear to provide more reliable and reproducible estimations of actual blood pressure and its long-term outcomes compared to office blood pressure measurements.¹ Indeed, the recent ACC/AHA guidelines⁴ on high blood pressure recommend more frequent use of out-of-office blood pressure measurements (ABPM or HBPM) to confirm diagnosis of hypertension; they also recommend titration of antihypertensive therapy based on them. These guidelines also recommend ABPM or HBPM in different scenarios to screen for white coat hypertension or masked hypertension.

Secondary causes of hypertension are usually treatable and should be screened, particularly in select indications. The ACC/AHA guidelines⁴ recommend looking for secondary causes of hypertension in:

- Those with early-onset hypertension (onset < 30 years of age)
- Those with abrupt-onset hypertension
- Those with drug-resistant or drug-induced hypertension
- Those with exacerbation of previously-controlled hypertension
- Those with accelerated or malignant hypertension
- Those with hypertension and disproportionate end-organ damage
- Elderly (≥ 65 years) with onset of diastolic hypertension
- Those with unprovoked or excessive hypokalemia.

When to initiate antihypertensive treatment? JNC 8 vs ACC/AHA recommendations

Lifestyle modifications are routinely recommended in all hypertensive patients with or without antihypertensive drug therapy. Evidence-based recommendations of the JNC 8³ propose initiation of antihypertensive drug therapy in all hypertensive adults ≥ 60 years of age at blood pressure $\geq 150/90$ mm Hg. In hypertensive subjects < 60 years of age, drug therapy is recommended at blood pressure $\geq 140/90$ mm Hg. Recommended target blood pressure goals are $< 150/90$ mm Hg in adults ≥ 60 years and $< 140/90$ mm Hg in adults < 60 years. In those with coexisting diabetes or CKD, antihypertensive drug therapy is recommended at blood pressure $> 140/90$ mm Hg, with the goal of reducing SBP to < 140 mm Hg and DBP to < 90 mm Hg.

The recent ACC/AHA guidelines (Figure 1)⁴ have also specified blood pressure thresholds for treatment initiation. Additionally, they recommend evaluation of risk of atherosclerotic cardiovascular disease (ASCVD) for guiding treatment decisions and improving its cost-effectiveness. These guidelines recommend lifestyle modifications (non-pharmacological therapy; Table 1) in all adults with blood pressure between 120-129/ < 80 mm Hg. Lifestyle modifications are also recommended in all adults with blood pressure between 130-139/80-89 mm Hg; in those with preexisting CV disease or high CV risk (10-year estimated risk $\geq 10\%$), additional antihypertensive drug therapy is recommended. In all hypertensive adults with blood pressure $\geq 140/90$ mm Hg, antihypertensive drug therapy should be initiated along with lifestyle modifications, irrespective of CV risk status. Since patients with diabetes have augmented CV risk, the ACC/AHA

Table 1. Lifestyle changes (non-pharmacological therapy): ACC/AHA recommendations

- Reduce weight (in overweight and obese patients)
- Increase physical activity (structural exercise program)
- Heart-healthy diet
- Restriction of sodium
- Potassium supplementation, preferably by dietary modifications
- Abstain from alcohol or moderation in alcohol consumption

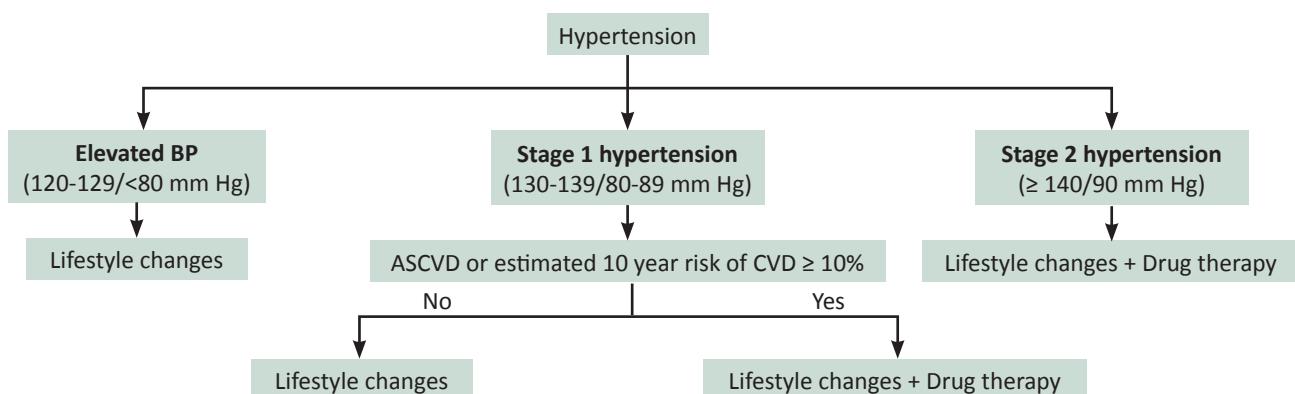
Sources: Carey RM, Whelton PK; 2017 ACC/AHA Hypertension Guideline Writing Committee. Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Synopsis of the 2017 American College of Cardiology/American Heart Association Hypertension Guideline. *Ann Intern Med*. 2018 Mar 6;168(5):351-358.

guidelines recommend initiation of antihypertensive drug therapy in all hypertensive patients with coexisting diabetes at blood pressure $> 130/80$ mm Hg; recommended blood pressure target in them should be $< 130/80$ mm Hg. For hypertensive patients with CKD, blood pressure target of $< 130/80$ mm Hg is recommended.

Pharmacological treatment

There is convincing evidence to show that optimizing blood pressure control using pharmacological antihypertensive therapy can reduce risk of coronary events, strokes, and heart failures.^{5,6} Several classes of antihypertensive drugs are currently available; including diuretics, RAS blockers (angiotensin converting enzyme inhibitors [ACE inhibitors] and angiotensin receptor blockers [ARBs]), calcium channel blockers (CCB), and beta-blockers.⁵ Results of the recent Systolic Pressure Intervention Trial (SPRINT) trial⁶ showed that intensive blood pressure lowering (SBP < 120 mm Hg) in hypertensive patients ≥ 50 years with increased CV risk but without diabetes or prior stroke resulted in 25% greater reduction in risk of combined outcomes of MI, stroke, heart failure, or CV deaths compared to standard blood pressure lowering (SBP < 140 mm Hg). The SPRINT trial was a landmark study as till its results were published, there was virtually no evidence to support lower target blood pressures ($< 130/80$ mm Hg) in patients aged ≥ 60 years. Although certain serious adverse events (hypotension, syncope, electrolyte abnormalities) of intensive blood pressure lowering were seen in the SPRINT trial, broadly there were definitive benefits of intensive compared to standard blood pressure lowering, particularly in reduction of fatal and non-fatal CV events. Although intensive blood pressure control is still not unequivocally recommended strategy

FIGURE 1 Specified blood pressure thresholds for antihypertensive treatment initiation according to 2017 ACC/AHA guidelines



Source: Carey RM, Whelton PK; 2017 ACC/AHA Hypertension Guideline Writing Committee. Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Synopsis of the 2017 American College of Cardiology/American Heart Association Hypertension Guideline. *Ann Intern Med.* 2018 Mar 6;168(5):351-358

in hypertensive patients, findings of the SPRINT trial prompted investigators to relook on the need to achieve lower blood pressure goals, at least in high-risk patients to optimize CV outcomes.

Different antihypertensive agents

Different classes of antihypertensive drugs are currently available for blood pressure lowering. In uncomplicated hypertension, first-line antihypertensive therapy should include a diuretic, RAS blocker (ACE inhibitors or ARBs) or CCB. Beta-blockers, although available since a long period of time for hypertension management, are currently not advocated as a first-line treatment option by most guidelines, except the 2013 hypertension management recommendations of the European Society of Hypertension (ESH).⁷

Diuretics, particularly thiazides, are commonly used front-line treatment options for hypertension, either alone or in combination with other antihypertensive agents. Both thiazides and thiazide-like drugs are widely used in hypertension management. They effectively reduce blood pressure and additionally mitigate risk of adverse CV outcomes.⁸ A recently published Cochrane meta-analysis⁹ showed that when used in low doses, thiazide diuretics reduce both morbidity and mortality outcomes in adult patients with moderate-to-severe hypertension. Nevertheless adverse effects associated with thiazides are concerning. Both randomized and observational studies have shown their association with metabolic abnormalities, including alteration in glucose and lipid metabolism.⁸ They can increase risk of type 2 diabetes, and caution should

therefore be exercised when using them, particularly in combination with beta-blockers. Hypokalemia is also a potential adverse effect associated with their use.¹⁰ Majority of metabolic adverse effects of thiazides are seen with high doses; therefore, low-dose diuretics are usually recommended.⁸

RAS blockers (ARBs and ACE inhibitors) are widely used treatment options for hypertension management, particularly in high-risk patients.¹¹ Compared to ARBs, role of ACE inhibitors is comparatively restricted due to their adverse effect profile (particularly cough) and limited ability to achieve target blood pressure control. Some ARBs, in contrast, provide more consistent 24-hour blood pressure control compared to ACE inhibitors.¹² ARBs additionally have a better tolerability profile and are associated with lower rates of treatment withdrawal.^{11,12} Recent evidence also indicates that ARBs may provide superior protection against recurrence of CV events in high-risk patients compared to ACE inhibitors.¹³ Both ARBs and ACE inhibitors also have an established role in reducing proteinuria, a surrogate marker for CKD progression and CV outcomes, in hypertensive patients with or without comorbid diabetes. These drugs reduce proteinuria to a greater extent than any other antihypertensive therapy.^{14,15}

The CCB are another class of commonly used antihypertensive agents. They are currently prescribed more frequently in combination with other antihypertensive agents (mainly RAS blockers) to achieve target blood pressure control.¹⁶ They are effective in blood pressure lowering, and additionally improve most CV outcomes, except heart failure.¹⁷ While dihydropyridine class

of CCB are primarily indicated for management of hypertension, and/or chronic, stable and vasospastic angina; non-dihydropyridines additionally have potent antiarrhythmic activity.¹⁶ It is noteworthy that CCB are not recommended for treating patients with heart failure with reduced ejection fraction (HFrEF), or in those at high risk of developing it. Moreover, CCB are deemed inferior to RAS blockers in patients with preexisting renal disease, and hence are not recommended as monotherapy in this category of patients.¹⁷

Combination antihypertensive therapy

Traditionally, physicians were wary of using antihypertensive therapy in combination for the fear of ill-effects of excessively reducing blood pressure, along with risk of incremental adverse effects, rendering the treatment intolerable. However, many subsequent studies^{18,19} confirmed difficulty in achieving satisfactory control of blood pressure on single antihypertensive therapy, citing requirement of at least two antihypertensive medications in most patients to achieve blood pressure control. The JNC 8 guideline³ confirms that an initial antihypertensive treatment strategy involving two drugs is acceptable in patients who are 20 mm Hg above systolic or 10 mm Hg above diastolic BP target; or when SBP is > 160 mm Hg or diastolic > 100 mm Hg. Similarly, the recent ACC/AHA recommendation⁴ on high blood pressure also advocate an early intensive approach, recommending initiation of two first-line antihypertensive agents in patients with stage 2 hypertension if SBP is > 20 mm Hg and DBP > 10 mm Hg above target.

Combination therapy can be administered either as free or fixed combination of antihypertensive drugs. Fixed-dose combinations (FDC) reduce pill burden, particularly in patients with hypertension and comorbid disorders, thereby improving treatment adherence. However, little difference has been shown in the efficacy of blood pressure control and incidence of adverse events when free and FDC antihypertensive therapy are compared.²⁰ Front-line antihypertensive drugs (ARBs, ACE inhibitors, CCB and thiazide diuretics) are widely used in different combinations for managing hypertensive patients. Majority of currently available FDC are diuretic-based. They have traditionally been associated with good efficacy profile, enhancing achievement of target blood pressure. They also have good tolerability.²¹

Choice of antihypertensive therapy

The JNC 8 guidelines³ recommend that in non-black population, including those with diabetes, antihypertensive

treatment should be initiated with a thiazide, ACE inhibitor/ARB, or a CCB, either alone or in combination. In contrast, they recommend initial choice to be made from amongst thiazide or CCB for managing hypertension in black population, including those with diabetes. These guidelines additionally recommend ACE inhibitors/ARB as the first-line antihypertensive therapy in hypertensive patients with CKD. In line with these recommendations, the recent ACC/AHA guidelines⁴ also recommend diuretics, ACE inhibitors/ARB, or CCB as front-line therapy in hypertension with diabetes; additionally suggesting preferable use of either ACE inhibitor or an ARB in the presence of albuminuria. In patients with CKD with albuminuria ≥ 300 mg/day or ≥ 300 mg/g albumin-to-creatinine ratio, ACE inhibitor is initially recommended, while ARB should be used in ACE-intolerant patients.

Novel treatment approaches for hypertension

Despite presence of a wide armamentarium of effective antihypertensive drugs, about 10–15% of hypertensive patients remain resistant to their antihypertensive therapy, despite being on three or more different classes of antihypertensive drugs, including a diuretic. Treatment of such resistant hypertension remains a challenge for the physicians worldwide.²² Mineralocorticoid receptor antagonists (MRA), particularly eplerenone, have a well-established role in heart failure management. Their role in management of treatment-resistant hypertension, particularly if caused by aldosterone breakthrough phenomenon, is currently being explored.²³ The recent PATHWAY-2 trial²⁴ confirmed effectiveness of spironolactone in treatment-resistant hypertension. Another novel approach being recently pursued for difficult to treat hypertension is activation of natriuretic peptide system. Dual angiotensin receptor-neprilysin inhibition (ARNI), using a valsartan and sacubitril combination (LCZ696), also appears to be an attractive antihypertensive treatment approach. Recent data has confirmed that LCZ696 reduces blood pressure more effectively compared to valsartan in patients with mild-to-moderate hypertension. More clinical trials however are necessary to validate such claims.²⁵ The brain aminopeptidases also modulate RAS pathway, and therefore they have a major role to play in blood pressure control. Theoretically, inhibition of brain aminopeptidase should serve as a novel treatment strategy for hypertension, although as with most other novel strategies, their role also remains to be comprehensively investigated.²² Many other

therapeutic strategies are currently under development and can provide valuable additions to the antihypertensive treatment armamentarium in the near future, thereby improving blood pressure control and significantly reducing risk of associated CV, renal and cerebrovascular complications.

CONCLUSION

Accurate and reliable blood pressure measurement is crucial for diagnosing hypertension. Recent introduction of aneroid and digital blood pressure measuring devices have significantly improved blood pressure detection, additionally reducing risk of mercury spill and toxicity. Additional ABPM and HBPM is also now being recommended as adjuvant to office blood pressure measurement, particularly for ruling out “white coat hypertension” and “masked hypertension”. Lifestyle modifications are recommended in all patients with hypertension. Several antihypertensive treatment options are currently available from which physicians can make their choice. Diuretics and RAS blockers are among the front-line treatment options, either used as mono- or combination therapy in hypertensive patients with or without diabetes. The RAS blockers are widely prescribed in patients with CKD due to their benefits in reducing proteinuria. While CCB are also deemed effective front-line antihypertensive therapy, they are currently more frequently being prescribed in combination with other antihypertensive therapies.

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| Usual dosages and frequency of common oral antihypertensive drugs | | | |
|-------------------------------------------------------------------|----------------------------|-------------------|-----------------------------|
| Class | Drug | Usual dose, range | Frequency |
| Thiazide or thiazide-type diuretics | | | |
| | Chlorthalidone | 12.5–25 mg/day | Once daily |
| | Hydrochlorothiazide | 25–50 mg/day | Once daily |
| | Indapamide | 1.25–2.5 mg/day | Once daily |
| | Metolazone | 2.5–10 mg/day | Once daily |
| ARBs | | | |
| | Azilsartan | 40–80 mg/day | Once daily |
| | Candesartan | 8–32 mg/day | Once daily |
| | Telmisartan | 20–80 mg/day | Once daily |
| | Olmesartan | 20–40 mg/day | Once daily |
| | Irbesartan | 150–300 mg/day | Once daily |
| | Valsartan | 80–320 mg/day | Once daily |
| | Losartan | 50–100 mg/day | Once/twice daily |
| | Eprosartan | 600–800 mg/day | Once/twice daily |
| ACE Inhibitors | | | |
| | Captopril | 12.5–150 mg/day | Twice/thrice daily |
| | Enalapril | 5–40 mg/day | Once/twice daily |
| | Ramipril | 2.5–10 mg/day | Once/twice daily |
| | Benazepril | 10–40 mg/day | Once/twice daily |
| | Lisinopril | 10–40 mg/day | Once daily |
| | Fosinopril | 10–40 mg/day | Once daily |
| | Perindopril | 4–16 mg/day | Once daily |
| | Moexipril | 7.5–30 mg/day | Once/twice daily |
| | Quinapril | 10–80 mg/day | Once/twice daily |
| | Trandolapril | 1–4 mg/day | Once daily |
| CCB (Dihydropyridines) | | | |
| | Amlodipine | 2.5–10 mg/day | Once daily |
| | Felodipine | 5–10 mg/day | Once daily |
| | Nifedipine LA | 60–120 mg/day | Once daily |
| | Nicardipine SR | 5–20 mg/day | Twice daily |
| | Nisoldipine | 30–90 mg/day | Once daily |
| | Isradipine | 5–10 mg/day | Twice daily |
| CCB (Non-dihydropyridines) | | | |
| | Diltiazem ER | 120–480 mg/day | Once daily |
| | Diltiazem SR | 180–360 mg/day | Twice daily |
| | Verapamil SR | 120–480 mg/day | Once/twice daily |
| | Verapamil IR | 40–80 mg/day | Thrice daily |
| | Verapamil-delayed onset ER | 100–480 mg/day | Once daily (in the evening) |

Source: Whelton PK, et al. A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA. Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. *Hypertension*. 2017;00:e000-e000.

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