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Hypertension Canada's 2016 CHEP Guidelines for Blood Pressure Measurement, Diagnosis, Assessment of Risk, Prevention and Treatment of Hypertension

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ABSTRACT

Hypertension Canada's CHEP Guidelines Task Force provides annually-updated, evidence-based recommendations to guide the diagnosis, assessment, prevention, and treatment of hypertension. This year, we present four new recommendations, as well as revisions to two previous recommendations. In the diagnosis and assessment of hypertension, automated office blood pressure, taken without patient-health provider interaction, is now recommended as the preferred method of measuring in-office blood pressure. Also, while a serum lipid panel remains part of the routine laboratory testing for patients with hypertension, both fasting and non-fasting collections are now considered acceptable. For individuals with secondary hypertension arising from primary hyperaldosteronism, adrenal vein sampling is recommended for those who are candidates for potential adrenalectomy. With respect to the treatment of hypertension, a new recommendation that has been added is for increasing dietary potassium to reduce blood pressure in those who are not at high risk for hyperkalemia. Furthermore, in selected high-risk patients, intensive blood pressure reduction to a target systolic blood pressure ≤120 mmHg should be considered to lower the risk of cardiovascular events. Finally, in hypertensive individuals with uncomplicated, stable angina pectoris, either a β blocker or calcium channel blocker may be considered for initial therapy. The specific evidence and rationale underlying each of these recommendations are discussed. Hypertension Canada's CHEP Guidelines Task Force will continue to provide annual updates.

KEY WORDS: hypertension, high blood pressure, guidelines, recommendations, diagnostic algorithm, electronic oscillometric devices, out-of-office blood pressure measurements, ambulatory blood pressure monitoring, home blood pressure monitoring, automated blood pressure, lipid profile, tobacco, smoking cessation, renovascular disease, renal artery stenosis, primary hyperaldosteronism, pheochromocytoma.

BRIEF SUMMARY

New and revised recommendations are presented. Automated office blood pressure is preferred for in-office measurement. Second, potassium is endorsed for blood pressure reduction. Third, adrenal vein sampling is recommended for individuals with primary hyperaldosteronism considering surgery. Fourth, in high-risk patients, a systolic target ≤120 mmHg should be considered. Fifth, non-fasting serum lipid panels are acceptable. Finally, in individuals with stable angina, a β blocker or calcium channel blocker may be considered for initial therapy.

EXECUTIVE SUMMARY

Objective: To provide updated 2016 evidence-based recommendations for the prevention, diagnosis, assessment, and treatment of hypertension in adults.

Methods: A search was performed in MEDLINE (up to August 2015) by a medical librarian. Reference lists were reviewed and experts were contacted to identify additional pertinent studies. Content and methodology experts reviewed and appraised relevant articles using standardized grading algorithms. For pharmacologic interventions, evidence from randomized controlled trials and systematic reviews of trials was preferred. Changes in cardiovascular morbidity and mortality, as well as total mortality were considered the primary outcomes of interest. For health behaviour management, blood pressure (BP) lowering was considered as the primary outcome. In those with chronic kidney disease, progressive renal impairment was also accepted as a clinically relevant outcome. All recommendations were graded according to the strength of the supporting evidence, and newly proposed recommendations or changes to existing recommendations were discussed at a consensus conference held on October 22, 2015 in Toronto, Canada. Proposed changes to the recommendations accepted at the consensus conference were subsequently voted upon by the 75 members of the Canadian Hypertension Education Program (CHEP) Recommendations Task Force. Recommendations that received at least 70% task force approval were then accepted as final.

Recommendations:

Diagnosis and Assessment

Two new recommendations and one modified recommendation have been introduced this year. First, automated office blood pressure (AOBP), taken without patient-health provider interaction using a fully-automated device, is now recommended as the preferred method of measuring in-office BP. Second, a modified recommendation has been made to the routine work-up for individuals with hypertension. A serum lipid panel (consisting of total cholesterol, low-density lipoprotein, high-density lipoprotein [HDL], non-HDL cholesterol, and triglycerides) is still recommended routinely, but may be drawn in either a fasting or non-fasting state. Finally, a new recommendation was introduced for subtype classification for individuals with secondary hypertension arising from primary hyperaldosteronism. In those who are candidates for potential adrenalectomy, assessment for lateralization should be performed using adrenal vein sampling.

Prevention and Treatment

This year, two new recommendations were added and another recommendation was modified. First, as a new recommendation, an increase in dietary potassium should be considered in individuals who are not at high risk for hyperkalemia as an effective way to reduce blood pressure. Second, in selected high-risk patients, intensive blood pressure reduction to target a systolic blood pressure ≤120 mmHg should be considered to lower the risk of cardiovascular events. As a revised recommendation, in individuals with stable angina pectoris (but without previous heart failure, myocardial infarction, or coronary artery bypass), either a β blocker or calcium channel blocker can be considered as equally acceptable choices for initial treatment.

Updates

CHEP will continue to update recommendations annually.

Introduction

Hypertension affects approximately 23% of Canadian adults and represents a major risk factor for cardiovascular disease, chronic kidney disease, and death; but it often remains clinically silent until complications arise.[1-3] Worldwide, high blood pressure (BP) affects over 40% of adults over the age of 25 and is the leading global risk factor for death or disability.[4, 5] In Canada, BP control rates have progressively improved from 13.2% in 1992 to 64.6% in 2007,[6] and most recently to 68.1% in 2012-2013.[1] In comparison, global BP control remains at 32.5%.[5]

With the goal of improving hypertension prevention, detection, assessment, and management in Canadians, CHEP, has been producing annually-updated, evidence-based recommendations for health care providers since 1999. Herein, we provide an updated list of recommendations for the care of adult patients with hypertension, as endorsed by the CHEP Recommendations Task Force, along with discussion of the supporting evidence for any revised or new additions for 2016. Details pertaining to previously established recommendations are available in prior publications,[6-31] and are also published online (guidelines.hypertension.ca). This year, we are also introducing new set of pediatric-specific recommendations (published separately).

Our recommendations are intended to guide health care providers but should not replace sound clinical judgment. Practitioners are advised to consider patient preferences, values, and clinical factors when determining how to best apply these recommendations to the bedside. Finally, although individual antihypertensive agents may be mentioned when discussing the current state of evidence, the reader should assume a class effect, unless otherwise stated.

Methods

Hypertension Canada's CHEP Recommendations Task Force is a multidisciplinary panel of content and methodological experts comprised of a Chair, a Central Review Committee, and 15 subgroups. Each subgroup addresses a distinct content area in the field of hypertension (see Supplementary Appendix A for the current CHEP membership list). Members of the Canadian Task Force on Preventive Health Care, Canadian Diabetes Association Guidelines Committee, Canadian Society of Nephrology, Canadian Stroke Network, Canadian Cardiovascular Society, and the Canadian Cardiovascular Harmonized National Guideline Endeavour Initiative regularly collaborate with CHEP members to facilitate harmonization of recommendations across many organizations. In many cases, CHEP Recommendations Task Force members serve as volunteers for multiple organizations.

Systematic literature searches current to August 2015 were performed by a librarian from the Cochrane Collaboration in MEDLINE/PubMed using text words and MeSH headings. Search terms included “hypertension[MeSH]”, “hypertens*[ti, ab]”, and “BP”; these were combined with topic-specific terms. Bibliographies of identified articles were also hand searched. Details of search strategies and retrieved articles are available upon request. Randomized controlled trials and systematic reviews of randomized controlled trials were reviewed for treatment recommendations, while cross-sectional and cohort studies were reviewed for evidence supporting diagnosis and informing prognosis.

Each subgroup examined the search results pertinent to its content area. Studies assessing relevant outcomes were selected for further review. Cardiovascular morbidity and mortality as well as total mortality outcomes were prioritized for pharmacotherapy studies. For health behaviour recommendations, BP was considered an acceptable surrogate and, in patients with chronic kidney disease, progressive renal impairment was considered to be a clinically important

outcome. Study characteristics and study quality were assessed using pre-specified, standardized algorithms developed by CHEP for the critical appraisal of randomized controlled trials and observational studies.[32]

Recommendations were graded according to the strength of their underlying evidence (for details, see Table S1 in Supplementary Materials), ranging from Grade A (strongest evidence, based on high-quality studies) to Grade D (weakest evidence, based on low power, imprecise studies, or expert opinion alone). In addition to classifying recommendations based on study quality, other grading schemes (e.g., Grading of Recommendations Assessment, Development and Evaluation (GRADE) [www.gradeworkinggroup.org]), also endorse use of the terms 'strong' and 'weak' to describe the extent to which the guideline creators are confident the benefits outweigh the risks. CHEP does not use these terms because all CHEP recommendations are considered to be 'strong' in nature (i.e., CHEP refrains from making 'weak' recommendations). Thus, the CHEP grading scheme refers only to the quality of evidence; all recommendations, regardless of grading, are felt to have benefits that strongly outweigh risks. For pharmacotherapy recommendations, as a general rule, CHEP considers evidence evaluating specific agents to be generalizable to a 'class effect'. For diuretic therapy, the term 'thiazides' refers to hydrochlorothiazide (or similar agents) and the term 'thiazide-like' refers to chlorthalidone and indapamide.

Subgroup members, considered content experts in their fields, were responsible for reviewing annual search results and, if indicated, drafting new recommendations or proposing changes to old recommendations. An independent Central Review Committee consisting of methodological experts with no industry affiliations independently reviewed, graded, and refined proposed recommendations, which were then presented at a consensus conference of the

Recommendations Task Force in Toronto, Canada on October 22, 2015. This meeting included the Chair, Central Review Committee, and members of all subgroups. Further revisions to proposed recommendations were based on these discussions. Notably, following our consensus conference, the Systolic Blood Pressure Intervention Trial (SPRINT) was released.[33] In light of its significant results, an expedited review of the SPRINT study was performed by the Recommendations Task Force, and therefore was included in this year's discussion.

All recommendations were finalized and submitted electronically to all 75 voting members of the CHEP Recommendations Task Force for approval. Members with potential conflicts of interest recused themselves from voting on specific recommendations (a list of conflicts is available as Supplementary Appendix B). Recommendations receiving over 70% approval were passed. The CHEP recommendations process is in accordance with the AGREE2 guidelines,[34] and has been externally reviewed. A summary of how the CHEP process aligns with AGREE2 can be found online (www.hypertension.ca/overview-process). Materials to assist with patient and public education based on these recommendations are freely available at: www.hypertension.ca.

The 2016 CHEP Diagnosis and Assessment Recommendations

I. Accurate measurement of BP

Recommendations

1. Health care professionals who have been specifically trained to measure BP accurately should assess BP in all adult patients at all appropriate visits to determine cardiovascular risk and monitor antihypertensive treatment (Grade D).

2. Use of standardized measurement techniques and validated equipment for all methods (non-automated office BP, automated office BP, home BP monitoring, and ambulatory BP monitoring) is recommended (Grade D; see Supplementary Table S2 [Office BP measurement, automated office BP], Section VII [Home BP monitoring], Section VIII [Ambulatory BP monitoring], Table 1 in Section VII [Home BP monitoring], and Table 2 in section VIII [Ambulatory BP monitoring]). Measurement using electronic (oscillometric) upper arm devices is preferred over auscultation (Grade C). (Unless specified otherwise, electronic [oscillometric] measurement should be used).

3. Four approaches can be used to assess BP:

i. Office BP measurement taken with a non-automated device (non-AOBP): A systolic BP (SBP) ≥140 mmHg or a diastolic BP (DBP) ≥90 mmHg is high, and an SBP between 130-139 mmHg and/or a DBP between 85-89 mmHg is high-normal (Grade C).

ii. Automated office BP (AOBP): AOBP is the preferred method of performing in-office BP measurement (Grade D) **(new recommendation)**. When using AOBP (see Supplemental Table S2, *AOBP*), a displayed mean SBP ≥135 mmHg or DBP ≥85 mmHg DBP is high (Grade D).

iii. Ambulatory BP monitoring: Using ambulatory BP monitoring (see Recommendations in Section VIII, *Ambulatory BP Monitoring*), patients can be diagnosed as hypertensive if the mean awake SBP is ≥135 mmHg or the DBP is ≥85 mmHg or if the mean 24-hour SBP is ≥130 mmHg or the DBP is ≥80 mmHg (Grade C).

iv. Home BP monitoring: (see Recommendations in Section VII, *Home BP Monitoring*) Patients can be diagnosed as hypertensive if the mean SBP is ≥135 mmHg or the DBP is ≥85 mmHg (Grade C). If the office BP measurement is high and the mean home BP is

<135/85 mm Hg, it is advisable to either repeat home monitoring to confirm the home BP is <135/85 mmHg or perform 24-hour ambulatory BP monitoring to confirm that the mean 24-hour ambulatory BP monitoring is <130/80 mmHg and the mean awake ambulatory BP monitoring is <135/85 mmHg before diagnosing white coat hypertension (Grade D).

Background. Building on our previous recommendation in favour of using electronic (oscillometric) upper arm devices,[31] this year we have introduced a new recommendation in support of AOBP as the preferred method of in-office blood pressure measurement. AOBP allows blood pressure to be measured using a fully automated electronic device without any patient-health provider interaction while the patient rests alone in a quiet room or private area (see Supplementary Table S2).

If AOBP is not used, care providers will typically need to remain in the room and perform sequential electronic measurements (because multiple measurements are recommended). The advantages of AOBP over this non-automated (non-AOBP) approach are that AOBP eliminates the risk of conversation during readings, reduces the risk of the white coat effect, and facilitates multiple measurements with each clinical encounter (and automatically calculates the mean). Measurements collected using AOBP appear to closely approximate mean awake ambulatory blood pressure levels.[34-41] AOBP measurements are also demonstrably consistent from visit-to-visit.[40, 42, 43] Furthermore, AOBP measurements do not appear to be significantly altered by the setting in which blood pressure is measured. Measurements taken in an ambulatory blood pressure monitoring unit, office waiting room, and physician's examination room have

been shown to be similar;[40, 44, 45] and, AOBP measurements obtained in a pharmacy and physician's office are likewise comparable.[46]

In addition to providing consistent and reliable readings, AOBP measurements are also useful in predicting the presence of end-organ damage (e.g., carotid intima-media thickness, left ventricular mass index, microalbuminuria).[47-49] It has also been recently demonstrated that elevated AOBP measurements are predictive of incident cardiovascular events.[50] In a recent 5-year longitudinal study of 3627 community-dwellers aged ≥65 years with untreated hypertension, the presence of an elevated SBP between 135 to 144 mmHg (measured using BpTRU in various community pharmacies) was associated with a 66% relative risk increase for developing an adverse cardiovascular event (hazard ratio [HR], 1.66; 95% confidence interval [CI], 1.09 to 2.54; compared to those with a SBP between 110 to 119 mmHg); similarly, a raised DBP between 80 to 89 mmHg was associated with a 72% increased risk (HR, 1.72; 95% CI, 1.21 to 2.45; compared to a DBP between 60 to 69 mmHg).[50] The generalizability of this study may potentially be limited by the older age of the participants (mean 74.2 years), measurement of blood pressure at community pharmacies, and exclusion of individuals already taking antihypertensive medications. Nonetheless this study provides evidence further supporting AOBP as the preferred method of in-office blood pressure measurement.

II. Criteria for diagnosis of hypertension and recommendations for follow-up (Figure 1)

Recommendations

1. At initial presentation, patients demonstrating features of a hypertensive urgency or emergency (Supplemental Table S3) should be diagnosed as hypertensive and require immediate management (Grade D). In all other patients, at least 2 more readings should be taken during the

same visit. If using non-AOBP measurement, the first reading should be discarded and the latter readings averaged. If using AOBP, the BP calculated and displayed by the device should be used.

2. If the visit 1 office BP measurement is high-normal (thresholds outlined in Section I, Recommendation 3) annual follow-up is recommended (Grade C).

3. If the visit 1 mean non-AOBP or AOBP measurement is high (thresholds outlined in Section I, Recommendation 3), a history and physical examination should be performed and, if clinically indicated, diagnostic tests to search for target organ damage (Supplemental Table S4) and associated cardiovascular risk factors (Supplemental Table S5) should be arranged within 2 visits. Exogenous factors that can induce or aggravate hypertension should be assessed and removed if possible (Supplemental Table S6). Visit 2 should be scheduled within 1 month (Grade D).

4. If the visit 1 mean non-AOBP or AOBP SBP is ≥180 mmHg and/or DBP is ≥110 mmHg then hypertension is diagnosed (Grade D).

5. If the visit 1 mean non-AOBP SBP is 140-179 mmHg and/or DBP is 90-109 mmHg OR the mean AOBP SBP is 135-179 mmHg and/or DBP is 85-109 mmHg, out-of-office BP measurements should be performed before visit 2 (Grade C).

i. Ambulatory BP monitoring is the recommended out-of-office measurement method (Grade D). Patients can be diagnosed with hypertension according to the thresholds outlined in Section I, Recommendation 3.

ii. Home BP monitoring is recommended if ambulatory BP monitoring is not tolerated, not readily available, or because of patient preference (Grade D). Patients can be

diagnosed with hypertension according to the thresholds outlined in Section I, Recommendation 3.

iii. If the out-of-office BP average is not elevated, white coat hypertension should be diagnosed and pharmacologic treatment should not be instituted (Grade C).

6. If the out-of-office measurement, although preferred, is NOT performed after visit 1, then patients can be diagnosed as hypertensive using serial office BP measurement visits if any of the following conditions are met:

i. At visit 2, mean office BP measurement (averaged across all visits) is ≥140 mmHg systolic and/or ≥90 mmHg diastolic in patients with macrovascular target organ damage, diabetes mellitus, or chronic kidney disease (glomerular filtration rate <60 mL/min/1.73m^2) (Grade D);

ii. At visit 3, mean office BP measurement (averaged across all visits) is ≥160 mmHg systolic or ≥100 mmHg diastolic;

iii. At visit 5, mean office BP measurement (averaged across all visits) is ≥140 mmHg systolic or ≥90 mmHg diastolic.

7. Investigations for secondary causes of hypertension should be initiated in patients with suggestive clinical and/or laboratory features (outlined in Sections V and VI) (Grade D).

8. If at the last diagnostic visit the patient is not diagnosed as hypertensive and has no evidence of macrovascular target organ damage, the patient's BP should be assessed at yearly intervals (Grade D).

9. Hypertensive patients actively modifying their health behaviors should be followed up at 3- to 6-month intervals. Shorter intervals (every 1 or 2 months) are needed for patients with higher BPs (Grade D).

10. Patients on antihypertensive drug treatment should be seen monthly or every 2 months, depending on the level of BP, until readings on 2 consecutive visits are below their target (Grade D). Shorter intervals between visits will be needed for symptomatic patients and those with severe hypertension, intolerance to antihypertensive drugs, or target organ damage (Grade D). When the target BP has been reached, patients should be seen at 3- to 6-month intervals (Grade D).

Background. There are no changes to these recommendations for 2016.

III. Assessment of overall cardiovascular risk in hypertensive patients

Recommendations

1. Global cardiovascular risk should be assessed. Multifactorial risk assessment models can be used to predict more accurately an individual's global cardiovascular risk (Grade A) and to use antihypertensive therapy more efficiently (Grade D). In the absence of Canadian data to determine the accuracy of risk calculations, avoid using absolute levels of risk to support treatment decisions (Grade C).
2. Consider informing patients of their global risk to improve the effectiveness of risk factor modification (Grade B). Consider also using analogies that describe comparative risk such as "cardiovascular age," "vascular age," or "heart age" to inform patients of their risk status (Grade B).

Background. There are no changes to these recommendations for 2016. Examples of freely available risk calculators include www.myhealthcheckup.com and www.score-canada.ca. The

latter is the **S**ystematic **C**erebrovascular and C**o**ronary **R**isk **E**valuation [SCORE]) risk calculator. Although not originally developed with Canadian data, Canadian cardiovascular disease prevalence and mortality risk have been integrated into the original SCORE risk engine to produce specific estimates for the Canadian population (SCORE Canada).

IV. Routine and optional laboratory tests for the investigation of patients with hypertension

Recommendations

1. Routine laboratory tests that should be performed for the investigation of all patients with hypertension include the following:

    i. Urinalysis (Grade D);

    ii. Blood chemistry (potassium, sodium, and creatinine) (Grade D);

    iii. Fasting blood glucose and/or glycated hemoglobin (A1c) (Grade D)

    iv. Serum total cholesterol, low-density lipoprotein, high-density lipoprotein (HDL), non-HDL cholesterol, and triglycerides (Grade D); lipids may be drawn fasting or non-fasting (Grade C) **(revised recommendation)**.

    v. Standard 12-lead electrocardiography (Grade C).

2. Assess urinary albumin excretion in patients with diabetes (Grade D).

3. All treated hypertensive patients should be monitored according to the current Canadian Diabetes Association guidelines for the new appearance of diabetes (Grade B).

4. During the maintenance phase of hypertension management, tests (including those for electrolytes, creatinine, and fasting lipids) should be repeated with a frequency reflecting the clinical situation (Grade D).

Background. This year, we provide a revised recommendation for the measurement of serum lipids. While a serum lipid panel still remains part of the routine laboratory work-up for individuals with hypertension,[31] a non-fasting lipid panel is now considered to be an acceptable method of measurement.

In 2012, a large Canadian community-based cross-sectional study was conducted, examining the association between fasting status and serum lipid levels in 209,180 individuals.[52] In that study, the investigators found that the duration of fasting (from 1 to >16 hours) had little association with measured lipid levels. Total cholesterol varied by less than 2% (with an average of 4.3 mmol/L after 1 hour of fasting compared to 4.5 mmol/L after a prolonged fast of 16 hours). Similarly, high-density lipoprotein (HDL) cholesterol varied by less than 2% (from 1.2 to 1.3 mmol/L) and low-density lipoprotein (LDL) cholesterol by less than 10% (from 2.3 to 2.6 mmol/L). However, there was a wider variation of nearly 20% associated with serum triglycerides levels with various durations of fasting. Altogether, these findings are consistent with those of other reports, also showing minimal differences in fasting compared to non-fasting cholesterol levels in the general population.[53, 54]

Multiple studies have demonstrated that non-fasting lipid levels are predictive of incident cardiovascular disease.[53-58] A Danish cohort of 9,319 individuals was followed prospectively for 14 years,[54] and demonstrated that individuals in the highest tertile of non-fasting total cholesterol were at increased risk for cardiovascular events compared to those in the in the lowest tertile (HR, 1.7; 95% CI, 1.1 to 2.6) with similar findings also seen for non-HDL cholesterol (HR, 2.3; 95% CI, 1.5 to 3.4) and LDL cholesterol (HR, 2.1; 95% CI, 1.4 to 3.1). In another study, based on the NHANES-III (National Health and Nutrition Examination Survey

III), 4299 pairs of fasting and non-fasting individuals (matched 1:1) were followed for a mean of 14 years. Regardless of whether LDL cholesterol was collected fasting or non-fasting, the levels were similarly predictive of cardiovascular mortality as well as all-cause mortality in a dose-dependent manner. This remained true for both individuals with and without diabetes.[53] Furthermore, using a centralized database of over 125 prospective studies, the Emerging Risk Factors Collaboration conducted a study of 302,430 participants (with a mean age of 58 years representing 2.79 million person-years at risk) and reported similar associations between death attributable to coronary heart disease and lipid levels (for HDL, non-HDL, and LDL), irrespective of fasting status.[57]

Finally, from a practical standpoint, performing non-fasting lipid assessments in routine clinical care may obviate many of the serious challenges associated with prolonged fasting, namely the possibility of decreased patient adherence, increased laboratory burden due to bolus testing in the morning, and preventable hypoglycemia among individuals with diabetes.[59-61]

V. Assessment for renovascular hypertension

Recommendations

1. Patients presenting with ≥2 of the following clinical clues listed below, suggesting renovascular hypertension, should be investigated (Grade D):

   i. Sudden onset or worsening of hypertension and age >55 or <30 years;

   ii. Presence of an abdominal bruit;

   iii. Hypertension resistant to ≥3 drugs;

   iv. Increase in serum creatinine level ≥30% associated with use of an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB);

v. Other atherosclerotic vascular disease, particularly in patients who smoke or have dyslipidemia;

vi. Recurrent pulmonary edema associated with hypertensive surges.

2. When available, the following tests are recommended to aid in the usual screening for renal vascular disease: captopril-enhanced radioisotope renal scan, Doppler sonography, magnetic resonance angiography, and computer tomography angiography (for those with normal renal function) (Grade B). Captopril-enhanced radioisotope renal scan is not recommended for those with chronic kidney disease (glomerular filtration rate <60 mL/min/1.73m^2) (Grade D).

Background. There are no changes to these recommendations for 2016.

VI. Endocrine hypertension

Recommendations

A. Hyperaldosteronism: screening and diagnosis:

1. Screening for hyperaldosteronism should be considered for the following patients (Grade D):

i. Hypertensive patients with unexplained spontaneous hypokalemia (K^+ <3.5 mmol/L) or marked diuretic-induced hypokalemia (K^+ <3.0 mmol/L);

ii. Patients with hypertension refractory to treatment with ≥3 drugs;

iii. Hypertensive patients found to have an incidental adrenal adenoma.

2. Screening for hyperaldosteronism should include assessment of plasma aldosterone and plasma renin activity or plasma renin (Supplemental Table S7).

3. For patients with suspected hyperaldosteronism (on the basis of the screening test, Supplemental Table S7, Item iii), a diagnosis of primary hyperaldosteronism should be

established by demonstrating inappropriate autonomous hypersecretion of aldosterone using at least one of the manoeuvres listed in Supplemental Table S7, Item iv. When the diagnosis is established, the abnormality should be localized using any of the tests described in Supplemental Table S7, Item v.

4. In patients with primary hyperaldosteronism and a definite adrenal mass who are eligible for surgery, adrenal venous sampling is recommended to assess for lateralization of aldosterone hypersecretion. Adrenal vein sampling should be performed exclusively by experienced teams working in specialized centres (Grade C) **(new recommendation)**.

B. Pheochromocytoma and paraganglioma: screening and diagnosis

1. If pheochromocytoma or paraganglioma is strongly suspected, the patient should be referred to a specialized hypertension center, particularly if biochemical screening tests (Supplemental Table S8) have already been found to be positive (Grade D).

2. The following patients should be considered for screening for pheochromocytoma or paraganglioma (Grade D):

i. Patients with paroxysmal, unexplained, labile, and/or severe (BP ≥180/ 110 mmHg) sustained hypertension refractory to usual antihypertensive therapy;

ii. Patients with hypertension and multiple symptoms suggestive of catecholamine excess (e.g., headaches, palpitations, sweating, panic attacks, and pallor);

iii. Patients with hypertension triggered by β-blockers, monoamine oxidase inhibitors, micturition, changes in abdominal pressure, surgery, or anesthesia;

iv. Patients with an incidentally discovered adrenal mass;

v. Patients with a predisposition to hereditary causes (e.g., multiple endocrine neoplasia 2A or 2B, von Recklinghausen neurofibromatosis type 1, or Von Hippel-Lindau disease);

vi. For patients with positive biochemical screening tests, localization of pheochromocytomas or paragangliomas should employ magnetic resonance imaging (preferable), computed tomography (if magnetic resonance imaging unavailable), and/or iodine I-131 meta-iodobenzylguanidine (MIBG) scintigraphy (Grade C for each modality).

Background. This year, we introduced a new recommendation to guide subtype classification for confirmed cases of primary hyperaldosteronism, as differentiation between unilateral and bilateral forms of aldosterone hypersecretion may have important treatment implications. Unilateral forms may be amenable to improvement or even cure with adrenalectomy. In contrast, mineralocorticoid receptor antagonists are the treatment of choice for bilateral hypersecretion. However, in certain cases where surgery is not possible or desired, subtype evaluation may be unnecessary, as treatment is uniformly medical, regardless of whether unilateral or bilateral disease is present (see Supplemental Table S7, item vi).

Numerous studies have reported significant discordance between conventional cross-sectional imaging with computed tomography (CT) and adrenal vein sampling (AVS).[62-67] In a prospective study of 203 patients with primary hyperaldosteronism, Young et al reported that the use of CT imaging alone would result in 22% of patients being incorrectly excluded for adrenalectomy while another 25% of individuals potentially receiving unnecessary surgery.[67] In another study by McAlister et al, 18 out of 27 individuals with confirmed primary hyperaldosteronism had adrenal masses visualized on CT; of these, only 13 had lateralization to the ipsilateral gland proven by AVS or surgery. Further, 5 out of 12 patients with bilateral

hypersecretion also had a visible adrenal mass on CT.[65] Indeed, a systematic review of 38 studies evaluating the performance of CT or magnetic resonance imaging (MRI) compared to AVS similarly found a striking high discrepancy rate of 37.8%.[68] Accordingly, reliance on cross-sectional imaging alone to determine lateralization may result in inappropriate treatment decisions.

Direct measurement of aldosterone secretion using AVS is widely considered to be the gold standard technique to determine lateralization. Even so, use of AVS may be limited because of technical challenges and reportedly high procedural failure rates, owing to difficulties in localizing the adrenal veins (especially on right side) because of small vessel size and variations in anatomy.[69] In a retrospective study of five centres using the German Conn's Registry, successful bilateral catheterization was only achieved in 30.5% of cases.[70] Performance appeared to be related to technical proficiency. Accordingly, when strictly performed by experienced teams in specialized centres with high throughput, some have reported impressive AVS success rates of >90%.[67, 69, 71, 72] Therefore, AVS should be exclusively performed at experienced centres to minimize the risk of potential failed catheterizations and unnecessary procedural complications.

VII. Home BP measurement

Recommendations

1. Home BP monitoring can be used in the diagnosis of hypertension (Grade C).

2. The use of home BP monitoring on a regular basis should be considered for patients with hypertension, particularly those with:

   i. Diabetes mellitus (Grade D);

ii. Chronic kidney disease (Grade C);

iii. Suspected non-adherence (Grade D);

iv. Demonstrated white coat effect (Grade C);

v. BP controlled in the office but not at home (masked hypertension) (Grade C).

3. When white coat hypertension is suggested by home BP monitoring, its presence should be confirmed by repeat home BP monitoring (Recommendation 7 in this section) or ambulatory BP monitoring before treatment decisions are made (Grade D).

4. Patients should be advised to purchase and use only home BP monitoring devices that are appropriate for the individual and have met standards of the Association for the Advancement of Medical Instrumentation, the most recent requirements of the British Hypertension Society protocol, or the International Protocol for validation of automated BP measuring devices. Patients should be encouraged to use devices with data recording capabilities or automatic data transmission to increase the reliability of reported home BP monitoring (Grade D).

5. Home SBP values ≥135 mmHg or DBP values ≥85 mmHg should be considered to be elevated and associated with an increased overall mortality risk (Grade C).

6. Health care professionals should ensure that patients who measure their BP at home have adequate training and, if necessary, repeat training in measuring their BP. Patients should be observed to determine that they measure BP correctly and should be given adequate information about interpreting these readings (Grade D).

7. Home BP monitoring for assessing white coat hypertension or sustained hypertension should be based on duplicate measures, morning and evening, for an initial 7-day period. First-day home BP values should not be considered (Grade D).

Background. There are no changes to these recommendations for 2016. A suggested, standardized protocol for home BP monitoring is presented in Table 1.

VIII. Ambulatory BP measurement

Recommendations

1. Ambulatory BP monitoring can be used in the diagnosis of hypertension (Grade C). Ambulatory BP monitoring should be considered when an office-induced increase in BP is suspected in treated patients with:

   i. BP that is not below target despite receiving appropriate chronic antihypertensive therapy (Grade C);

   ii. Symptoms suggestive of hypotension (Grade C);

   iii. Fluctuating office BP readings (Grade D).

2. Ambulatory BP monitoring upper arm devices that have been validated independently using established protocols must be used (see www.dableducational.org) (Grade D).

3. Therapy adjustment should be considered in patients with a mean 24-hour ambulatory BP monitoring SBP of ≥130 mmHg and/or DBP of ≥80 mmHg, or a mean awake SBP of ≥135 mmHg and/or DBP of ≥85 mmHg (Grade D).

4. The magnitude of changes in nocturnal BP should be taken into account in any decision to prescribe or withhold drug therapy based upon ambulatory BP monitoring (Grade C) because a decrease in nocturnal BP of <10% is associated with increased risk of cardiovascular events.

Background. There are no changes to these recommendations for 2016. A suggested, standardized protocol for ambulatory BP monitoring is presented in Table 2.

IX. Role of echocardiography

Recommendations

1. Routine echocardiographic evaluation of all hypertensive patients is not recommended (Grade D).

2. An echocardiogram for assessment of left ventricular hypertrophy is useful in selected cases to help define the future risk of cardiovascular events (Grade C).

3. Echocardiographic assessment of left ventricular mass, as well as of systolic and diastolic left ventricular function is recommended for hypertensive patients suspected to have left ventricular dysfunction or coronary artery disease (Grade D).

4. Patients with hypertension and evidence of heart failure should have an objective assessment of left ventricular ejection fraction, either by echocardiogram or nuclear imaging (Grade D).

Background. There are no changes to these recommendations for 2016.

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Please note, hereafter, all treatment thresholds and targets refer to office BP measurements, as most of the supporting evidence is derived from studies using this method of BP measurement. Please refer to the *Diagnosis and Assessment Recommendations,* section II (*Criteria for Diagnosis of Hypertension and Recommendations for Follow-up*) for corresponding values using other measurement methods. A summary of the potential factors that should be considered when selecting specific drug therapy for individualized treatment is presented in Table 3.

I. Health behaviour management

Recommendations

A. Physical exercise

1. For non-hypertensive or stage 1 hypertensive individuals, the use of resistance or weight training exercise (such as free weight lifting, fixed-weight lifting, or handgrip exercise) does not adversely influence BP (Grade D). For non-hypertensive individuals (to reduce the possibility of becoming hypertensive) or for hypertensive patients (to reduce their BP), prescribe the accumulation of 30-60 minutes of moderate intensity dynamic exercise (e.g., walking, jogging, cycling or swimming) 4-7 days per week in addition to the routine activities of daily living (Grade D). Higher intensities of exercise are not more effective (Grade D).

B. Weight reduction

1. Height, weight, and waist circumference should be measured and body mass index calculated for all adults (Grade D).

2. Maintenance of a healthy body weight (body mass index 18.5 to 24.9 kg/m^2, and waist circumference <102 cm for men and <88 cm for women) is recommended for non-hypertensive individuals to prevent hypertension (Grade C) and for hypertensive patients to reduce BP (Grade B). All overweight hypertensive individuals should be advised to lose weight (Grade B).

3. Weight loss strategies should employ a multidisciplinary approach that includes dietary education, increased physical activity, and behavioral intervention (Grade B).

C. Alcohol consumption

1. To reduce BP, healthy adults should limit alcohol consumption to ≤2 drinks per day, and consumption should not exceed 14 standard drinks per week for men and 9 standard drinks per week for women (Grade B). (Note: One standard drink is considered to be equivalent of 13.6 g or 17.2 ml of ethanol or approximately 44 mL [1.5 oz] of 80-proof [40%] spirits, 355 mL [12 oz] of 5% beer, or 148 mL [5 oz] of 12% wine).

D. Dietary recommendations

1. It is recommended that hypertensive patients and normotensive individuals at increased risk of developing hypertension consume a diet that emphasizes fruits, vegetables, low-fat dairy products, dietary and soluble fiber, whole grains, and protein from plant sources that is reduced in saturated fat and cholesterol (Dietary Approaches to Stop Hypertension [DASH] diet;[73-76] Supplemental Table S9) (Grade B).

E. Sodium intake

1. To decrease BP, consider reducing sodium intake towards 2000 mg (5g of salt or 87 mmol of sodium) per day (Grade A).

F. Calcium and magnesium intake

1. Supplementation of calcium and magnesium is not recommended for the prevention or treatment of hypertension (Grade B).

G. Potassium intake

1. In patients not at risk of hyperkalemia (see Table 4), increase dietary potassium intake to reduce blood pressure (Grade A) **(new recommendation)**.

H. Stress management

1. In hypertensive patients in whom stress may be contributing to high BP, stress management should be considered as an intervention (Grade D). Individualized cognitive-behavioural interventions are more likely to be effective when relaxation techniques are used (Grade B).

Background. This year, we introduced a new recommendation supporting an increase in dietary potassium to lower blood pressure. Supporting evidence for this recommendation comes from several systematic reviews and meta-analyses demonstrating a consistent association between increased potassium intake and blood pressure reduction. The most rigorous of these reviews was a meta-analysis of 22 randomized controlled trials by Aburto et al, which demonstrated that increased potassium intake reduced systolic blood pressure by 3.49 mm Hg (95% CI, 1.82 to 5.15 mmHg) and DBP by 1.96 mm Hg (95% CI, 0.86 to 3.06 mmHg).[77] Notably, blood pressure reduction was only seen in those with hypertension. There was no significant dose response according to the amount of potassium consumed. However, blood pressure reduction appeared to be greatest in those who consumed the greatest amount of salt (change in SBP of -6.9 vs. -2.0 in those with high [4 g/d] vs. low [<2 g/d] sodium intake). While the magnitude of blood pressure reduction is largest when the sodium intake is high, there still appears to be evidence of additive benefit when dietary interventions combine potassium increases with sodium reduction strategies.[73]

The magnitude of expected blood pressure reduction appears to be similar regardless of whether a potassium intervention is delivered through dietary changes or prescribed supplements.[77] If possible, however, we recommend dietary modification as the preferred method of increasing potassium intake because of the additional nutritional benefits of whole foods over prescribed supplements. When appropriate, patients with hypertension should be encouraged to consume foods with higher potassium content (e.g., fresh fruits, vegetables, and legumes). Overall, potassium interventions appear to be largely safe with no increase in reported adverse events.[77] However, it should be acknowledged that the generalizability of existing studies is limited by stringent exclusion criteria (e.g., excluding those with impaired urinary potassium excretion from renal failure or use of medications which predispose to hyperkalemia).[77] As such, although the literature broadly supports increasing potassium intake to lower blood pressure, caution should be exercised in those at higher risk of developing hyperkalemia (Table 4).

II. Indications for drug therapy for adults with hypertension without compelling indications for specific agents

Recommendations

1. Antihypertensive therapy should be prescribed for average DBP measurements of ≥100 mmHg (Grade A) or average SBP measurements of ≥160 mmHg (Grade A) in patients without macrovascular target organ damage or other cardiovascular risk factors.
2. Antihypertensive therapy should be strongly considered if DPB readings average ≥90 mmHg in the presence of macrovascular target organ damage or other independent cardiovascular risk factors (Grade A).

3. Antihypertensive therapy should be strongly considered if SBP readings average ≥140 mmHg in the presence of macrovascular target organ damage (Grade C for 140-160 mmHg; Grade A for >160 mmHg).

4. Antihypertensive therapy should be considered in all patients meeting indications 1-3 in this section, regardless of age (Grade B). Caution should be exercised in elderly patients who are frail.

5. In the very elderly (aged ≥80 years) who do not have diabetes or target organ damage, the SBP threshold for initiating drug therapy is ≥160 mm Hg (Grade C).

Background. There are no changes to these recommendations for 2016.

III. Choice of therapy for adults with hypertension without compelling indications for specific agents

Recommendations

A. Recommendations for individuals with diastolic and/or systolic hypertension

1. Initial therapy should be monotherapy with a thiazide/thiazide-like diuretic (Grade A), a β blocker (in patients younger than 60 years, Grade B), an ACE inhibitor (in non-black patients, Grade B), a long-acting calcium channel blocker (CCB) (Grade B); or an ARB (Grade B). If there are adverse effects, another drug from this group should be substituted. Hypokalemia should be avoided in patients treated with thiazide/thiazide-like diuretic monotherapy (Grade C).

2. Additional antihypertensive drugs should be used if target BP levels are not achieved with standard-dose monotherapy (Grade B). Add-on drugs should be chosen from first-line choices. Useful choices include a thiazide/thiazide-like diuretic or CCB with either: ACE inhibitor, ARB

or β blocker (Grade B for the combination of thiazide/thiazide-like diuretic and a dihydropyridine CCB; Grade C for the combination of dihydropyridine CCB and ACE inhibitor; and Grade D for all other combinations). Caution should be exercised in combining a non-dihydropyridine CCB and a β blocker (Grade D). The combination of an ACE inhibitor and an ARB is not recommended (Grade A).

3. Combination therapy using 2 first-line agents may also be considered as initial treatment of hypertension (Grade C) if SBP is 20 mmHg greater than target or if DBP is 10 mmHg greater than target. However, caution should be exercised in patients in whom a decrease in BP from initial combination therapy is more likely to occur or in whom it would be poorly tolerated (e.g. elderly patients).

4. If BP is still not controlled with a combination of 2 or more first-line agents, or there are adverse effects, other antihypertensive drugs may be added (Grade D).

5. Possible reasons for poor response to therapy (Supplemental Table S10) should be considered (Grade D).

6. α-Blockers are not recommended as first-line agents for uncomplicated hypertension (Grade A); β blockers are not recommended as first-line therapy for uncomplicated hypertension in patients 60 years of age or older (Grade A); and ACE inhibitors are not recommended as first-line therapy for uncomplicated hypertension in black patients (Grade A). However, these agents may be used in patients with certain comorbid conditions or in combination therapy.

Background. There are no changes to these recommendations for 2016.

B. Recommendations for individuals with isolated systolic hypertension

1. Initial therapy should be single-agent therapy with a thiazide/thiazide-like diuretic (Grade A), a long-acting dihydropyridine CCB (Grade A), or an ARB (Grade B). If there are adverse effects, another drug from this group should be substituted. Hypokalemia should be avoided in patients treated with thiazide/thiazide-like diuretic monotherapy (Grade C).

2. Additional antihypertensive drugs should be used if target BP levels are not achieved with standard-dose monotherapy (Grade B). Add-on drugs should be chosen from first-line options (Grade D).

3. If BP is still not controlled with a combination of 2 or more first-line agents, or there are adverse effects, other classes of drugs (such as α-blockers, ACE inhibitors, centrally acting agents, or non-dihydropyridine CCBs) may be added or substituted (Grade D).

4. Possible reasons for poor response to therapy (Supplemental Table S10) should be considered (Grade D).

5. α-Blockers are not recommended as first-line agents for uncomplicated isolated systolic hypertension (Grade A); and β blockers are not recommended as first-line therapy for isolated systolic hypertension in patients aged ≥60 years (Grade A). However, both agents may be used in patients with certain comorbid conditions or in combination therapy.

Background. There are no changes to these recommendations for 2016.

IV. Global vascular protection therapy for adults with hypertension without compelling indications for specific agents

Recommendations

1. Statin therapy is recommended in hypertensive patients with 3 or more cardiovascular risk factors as defined in Supplemental Table S11 (Grade A in patients >40 years) or with established atherosclerotic disease (Grade A regardless of age).

2. Consideration should be given to the addition of low dose acetylsalicylic acid (ASA) therapy in hypertensive patients ≥50 years of age (Grade B). Caution should be exercised if BP is not controlled (Grade C).

3. Tobacco use status of all patients should be updated on a regular basis and health care providers should clearly advise patients to quit smoking (Grade C).

4. Advice in combination with pharmacotherapy (e.g. varenicline, bupropion, nicotine replacement therapy) should be offered to all smokers with a goal of smoking cessation (Grade C).

5. For high-risk patients (Table 5), aged ≥50 years, with systolic BP levels ≥130 mmHg, intensive management to target a systolic BP ≤120 mmHg should be considered. Intensive management should be guided by automated office BP measurements (see *Diagnosis and Assessment Recommendations*, Section I [Accurate measurement of BP], and Supplemental Table S2 [Recommended Technique for Automated Office Blood Pressure]). Patient selection for intensive management is recommended and caution should be taken in certain high-risk groups (Table 6) (Grade B) **(new recommendation)**.

Background. This year, we have added a new recommendation to consider intensive BP control, targeting a SBP ≤120 mmHg in selected high-risk patients.

Systolic Blood Pressure Intervention Trial (SPRINT) was a randomized controlled trial that enrolled 9631individuals at high risk for cardiovascular disease (but without diabetes or

prior stroke) and randomized them to receive either intensive treatment (targeting a SBP <120 mmHg) or standard control (targeting a SBP <140 mmHg).[33] The trial was terminated after only 3.26 years because of a significant reduction in adverse cardiovascular events with intensive BP control that was detected before the end of the planned 5 years of follow-up. For the primary outcome of interest (a composite of myocardial infarction, acute coronary syndrome not resulting in myocardial infarction, stroke, acute decompensated heart failure, or death from cardiovascular causes), individuals receiving intensive treatment had an event rate of 1.65%/year compared to 2.19%/year in those assigned to standard treatment (HR, 0.75; 95% CI, 0.64 to 0.89). Among individuals with normal kidney function at baseline, intensive control was associated with an increased risk of renal deterioration compared to standard treatment (HR, 3.49; 95% CI, 2.44 to 5.10). Serious adverse events commonly occurred but were similar in both groups (38.3% vs. 37.1% for intensive- vs. standard-treatment; p=0.25). While our new treatment recommendation is largely based on the findings of SPRINT, it is also consistent with those of two recent meta-analyses of randomized controlled trials, likewise demonstrating a strong linear association between lower SBP targets and a reduction in major adverse cardiovascular events.[78, 79]

In selected high-risk patients who may potentially benefit from lower BP targets, several major considerations should be made before implementing an intensive treatment strategy. First, risk evaluation should be primarily informed by the inclusion criteria used in the SPRINT trial (Table 5).[33] Second, the risks and benefits of intervention should be carefully weighed, as patients with hypertension are at risk for both adverse vascular events *and* adverse treatment effects. Caution should be exercised in the setting of clinical conditions in which evidence supporting lower SBP targets <120 mmHg remains limited, and therefore intensive BP lowering is more difficult to justify in light of the increased risk of adverse treatment effects (Table 6).

Third, treatment should be guided by automated office BP measurements (see *Diagnosis and Assessment Recommendations*, Section I [Accurate measurement of BP], and Supplemental Table S2 [Recommended Technique for Automated Office Blood Pressure]), as was the case in the SPRINT trial.[33] Finally, patients should be prepared for more clinical encounters, monitoring, and medication usage. Individuals receiving intensive treatment in SPRINT were followed monthly until target BP levels were achieved. On average, they were prescribed 2.7 antihypertensive agents, compared to 1.8 agents in the standard control group.[33] While SBP targets <120 mmHg are beneficial in carefully selected cases, intensive treatment also incurs greater healthcare utilization and potential treatment risks.

V. Goals of therapy for adults with hypertension without compelling indications for specific agents

Recommendations

1. The SBP treatment goal is a pressure level of <140 mmHg (Grade C). The DBP treatment goal is a pressure level of <90 mmHg (Grade A).

2. In the very elderly (age ≥80 years), the SBP target is <150 mm Hg (Grade C)**.**

Background. There are no changes to these recommendations for 2016.

VI. Treatment of hypertension in association with ischemic heart disease

Recommendations

A. Recommendations for hypertensive patients with coronary artery disease (CAD)

1. For most hypertensive patients with CAD, an ACE inhibitor or ARB is recommended (Grade A).

2. For hypertensive patients with CAD, but without coexisting systolic heart failure, the combination of an ACE inhibitor and ARB is not recommended (Grade B).

3. For high-risk hypertensive patients, when combination therapy is being used, choices should be individualized. The combination of an ACE inhibitor and a dihydropyridine CCB is preferable to an ACE inhibitor and a thiazide/thiazide-like diuretic in selected patients (Grade A).

4. For patients with stable angina pectoris but without prior heart failure, myocardial infarction, or coronary artery bypass surgery, either a β-blocker or calcium channel blocker can be used as initial therapy (Grade B) **(revised recommendation)**.

5. Short-acting nifedipine should not be used (Grade D).

6. When decreasing SBP to target levels in patients with established CAD (especially if isolated systolic hypertension is present), be cautious when the DBP is ≤60 mmHg because of concerns that myocardial ischemia may be exacerbated (Grade D).

Background. We have revised our previous recommendations in this section with minor wording changes to improve clarity. Additionally, this year, a content revision was made in support of using either a β blocker or calcium channel blocker for initial therapy in adults with hypertension and stable angina, but without prior heart failure, myocardial infarction, or coronary artery bypass surgery. This revision is based on a body of evidence that suggests that both β blockers and calcium channel blockers are similarly effective in preventing major adverse cardiovascular events in patients with chronic, stable coronary disease, and it harmonizes our recommendations with those of the recent Canadian Cardiovascular Society.[80]

The largest contributor to this evidence was the International Verapamil-Trandolapril Study (INVEST), which enrolled 22,576 patients, aged ≥50 years, with hypertension and stable coronary artery disease, and randomized participants to receive either verapamil or atenolol to target a blood pressure of <140/90 mmHg (or <130/85 mmHg in patients with diabetes or chronic kidney disease).[81] A second agent could be added if patients did not achieve target; trandolapril was added for those initially randomized to verapamil, and hydrochlorothiazide was added for those in the atenolol group. Trandolapril was also added to atenolol if patients had a history of diabetes or CKD. The primary outcome was a composite of death, non-fatal MI, and non-fatal stroke. After 2.3 years of follow-up, similar blood pressure reductions were seen in both groups (-18.7/-10.0 mmHg with verapamil vs. -19.0/-10.2 mmHg with atenolol). The average number of medications required to achieve target blood pressure was the same in both groups (mean, 1.7 medications). The overall event rates were also similar in both groups, with a total of 2380 outcome events confirmed: 1171 in the verapamil group and 1209 in those receiving atenolol. The relative risk for the primary outcome was 0.98 (95% CI, 0.90 to 1.06) with no significant differences detected between those treated with verapamil compared to atenolol.

The findings of INVEST are congruent with two other smaller trials, the Angina Pectoris Study in Stockholm (APSIS) and the Total Ischemic Burden European Trial (TIBET).[82, 83] These two studies enrolled and randomized 809 and 682 patients, respectively, with stable angina to either a β blocker (i.e., metoprolol in APSIS and atenolol in TIBET) or a calcium channel blocker (verapamil in APSIS and nifedipine in TIBET). Both trials demonstrated a comparable efficacy between β blockers and calcium channel blockers in preventing major adverse cardiovascular events in patients with stable coronary disease. Notably, however, neither trial

required hypertension to be present for study inclusion. Only a quarter of participants in APSIS had hypertension compared to around half of those in TIBET. Nonetheless, the existing evidence as a whole supports the use of either a β blocker or calcium channel blocker as initial therapy in those with stable coronary disease.

B. Recommendations for patients with hypertension who have had a recent myocardial infarction

1. Initial therapy should include both a β-blocker and an ACE inhibitor (Grade A).
2. An ARB can be used if the patient is intolerant of an ACE inhibitor (Grade A in patients with left ventricular systolic dysfunction).
3. CCBs may be used in patients after myocardial infarction when β-blockers are contraindicated or not effective. Nondihydropyridine CCBs should not be used when there is heart failure, evidenced by pulmonary congestion on examination or radiography (Grade D).

Background. There are no changes to these recommendations for 2016.

VII. Treatment of hypertension in association with heart failure

Recommendations

1. In patients with systolic dysfunction (ejection fraction <40%), ACE inhibitors (Grade A) and β-blockers (Grade A) are recommended for initial therapy. Aldosterone antagonists (mineralocorticoid receptor antagonists) may be added for patients with a recent cardiovascular hospitalization, acute myocardial infarction, elevated B-type natriuretic peptide or N-terminal (NT) pro-B-type natriuretic peptide level, or New York Heart Association Class II-IV symptoms

(Grade A). Careful monitoring for hyperkalemia is recommended when adding an aldosterone antagonist to ACE inhibitor or ARB. Other diuretics are recommended as additional therapy if needed (Grade B for thiazide/thiazide-like diuretics for BP control, Grade D for loop diuretics for volume control). Beyond considerations of BP control, doses of ACE inhibitors or ARBs should be titrated to those found to be effective in trials unless adverse effects become manifest (Grade B).

2. An ARB is recommended if ACE inhibitors are not tolerated (Grade A).

3. A combination of hydralazine and isosorbide dinitrate is recommended if ACE inhibitors and ARBs are contraindicated or not tolerated (Grade B).

4. For hypertensive patients whose BP is not controlled, an ARB may be added to an ACE inhibitor and other antihypertensive drug treatment (Grade A). Careful monitoring should be used if combining an ACE inhibitor and an ARB because of potential adverse effects such as hypotension, hyperkalemia, and worsening renal function (Grade C). Additional therapies may also include dihydropyridine CCBs (Grade C).

Background. There are no changes to these recommendations for 2016.

VIII. Treatment of hypertension in association with stroke

Recommendations

A. BP management in acute stroke (onset to 72 hours)

1. For patients with ischemic stroke not eligible for thrombolytic therapy, treatment of hypertension in the setting of acute ischemic stroke or transient ischemic attack should not be routinely undertaken (Grade D). Extreme BP increases (e.g., SBP >220 mmHg or DBP >120

mmHg) may be treated to reduce the BP by approximately 15% (Grade D), and not more than 25%, over the first 24 hours with gradual reduction thereafter (Grade D). Avoid excessive lowering of BP because this might exacerbate existing ischemia or might induce ischemia, particularly in the setting of intracranial arterial occlusion or extracranial carotid or vertebral artery occlusion (Grade D). Pharmacological agents and routes of administration should be chosen to avoid precipitous decreases in BP (Grade D).

2. For patients with ischemic stroke eligible for thrombolytic therapy, very high BP (>185/110 mmHg) should be treated concurrently in patients receiving thrombolytic therapy for acute ischemic stroke to reduce the risk of secondary intracranial hemorrhage (Grade B).

B. BP management after acute stroke

1. Strong consideration should be given to the initiation of antihypertensive therapy after the acute phase of a stroke or transient ischemic attack (Grade A).

2. After the acute phase of a stroke, BP-lowering treatment is recommended to a target of consistently <140/90 mmHg (Grade C).

3. Treatment with an ACE inhibitor and thiazide/thiazide-like diuretic combination is preferred (Grade B).

4. For patients with stroke, the combination of an ACE inhibitor and ARB is not recommended (Grade B).

Background. There are no changes to these recommendations for 2016.

IX. Treatment of hypertension in association with left ventricular hypertrophy

Recommendations

1. Hypertensive patients with left ventricular hypertrophy should be treated with antihypertensive therapy to lower the rate of subsequent cardiovascular events (Grade C).

2. The choice of initial therapy can be influenced by the presence of left ventricular hypertrophy (Grade D). Initial therapy can be drug treatment using ACE inhibitors, ARBs, long-acting CCBs or thiazide/thiazide-like diuretics. Direct arterial vasodilators such as hydralazine or minoxidil should not be used.

Background. There are no changes to these recommendations for 2016.

X. Treatment of hypertension in association with non-diabetic chronic kidney disease

Recommendations

1. For patients with nondiabetic chronic kidney disease, target BP is <140/90 mmHg (Grade B).

2. For patients with hypertension and proteinuric chronic kidney disease (urinary protein >500 mg per 24 hours or albumin to creatinine ratio >30 mg/mmol), initial therapy should be an ACE inhibitor (Grade A) or an ARB if there is intolerance to ACE inhibitors (Grade B).

3. Thiazide/thiazide-like diuretics are recommended as additive antihypertensive therapy (Grade D). For patients with chronic kidney disease and volume overload, loop diuretics are an alternative (Grade D).

4. In most cases, combination therapy with other antihypertensive agents might be needed to reach target BP levels (Grade D).

5. The combination of an ACE inhibitor and ARB is not recommended for patients with non-proteinuric chronic kidney disease (Grade B).

Background. There are no changes to these recommendations for 2016.

XI. Treatment of hypertension in association with renovascular disease

Recommendations

1. Patients with hypertension attributable to atherosclerotic renal artery stenosis (RAS) should be primarily medically managed because renal angioplasty and stenting offers no benefit over optimal medical therapy alone (Grade B).
2. Renal artery angioplasty and stenting for atherosclerotic hemodynamically significant renal artery stenosis could be considered for patients with uncontrolled hypertension resistant to maximally tolerated pharmacotherapy, progressive renal function loss, and acute pulmonary edema (Grade D).

Background. There are no changes to these recommendations for 2016.

XII. Treatment of hypertension in association with diabetes mellitus

Recommendations

1. Persons with diabetes mellitus should be treated to attain SBP of <130 mmHg (Grade C) and DBP of <80 mmHg (Grade A) (these target BP levels are the same as the BP treatment thresholds). Combination therapy using 2 first-line agents may also be considered as initial treatment of hypertension (Grade B) if SBP is 20 mmHg greater than target or if DBP is 10 mmHg greater than target. However, caution should be exercised in patients in whom a

substantial decrease in BP is more likely or poorly tolerated (e.g., elderly patients and patients with autonomic neuropathy).

2. For persons with cardiovascular or kidney disease, including microalbuminuria, or with cardiovascular risk factors in addition to diabetes and hypertension, an ACE inhibitor or an ARB is recommended as initial therapy (Grade A).

3. For persons with diabetes and hypertension not included in other recommendations in this section, appropriate choices include (in alphabetical order): ACE inhibitors (Grade A), ARBs (Grade B), dihydropyridine CCBs (Grade A), and thiazide/thiazide-like diuretics (Grade A).

4. If target BP levels are not achieved with standard-dose monotherapy, additional antihypertensive therapy should be used. For persons in whom combination therapy with an ACE inhibitor is being considered, a dihydropyridine CCB is preferable to a thiazide/thiazide-like diuretic (Grade A).

Background. There are no changes to these recommendations for 2016.

XIII. Adherence strategies for patients

Recommendations

1. Adherence to an antihypertensive prescription can be improved by a multipronged approach (Supplemental Table S12).

Background. There are no changes to these recommendations for 2016.

XIV. Treatment of secondary hypertension due to endocrine causes

Recommendations

1. Treatment of hyperaldosteronism and pheochromocytoma are outlined in Supplemental Tables S7 and S8, respectively.

Background. There are no changes to these recommendations for 2016.

Implementation

Considerable ongoing effort is invested into knowledge translation by the CHEP Implementation Task Force to enhance uptake of our recommendations. Recognizing the challenge in reaching a large number of providers who care for patients with hypertension, we employ a large number of strategies to increase the dissemination and uptake of our recommendations as broadly as possible; these include knowledge exchange forums, targeted educational materials for primary care providers and patients, "Train the Trainer" teaching sessions, as well as slide kits and summary documents which are freely available online (www.hypertension.ca). Documents are available in French and English, and some documents are additionally translated into other languages. The implementation task force receives feedback from end-users to continually improve guideline processes and content.

The CHEP Outcomes Research Task Force conducts hypertension surveillance studies and reviews existing Canadian health surveys to identify gaps between current and best practices.

Future Directions

The present paper represents the 16th iteration of the annually updated CHEP recommendations for the management of hypertension. The Recommendations Task Force plans to continue our systematic reviews of the literature and to update our recommendations on an annual basis.

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Disclosures

Please see Supplemental Appendix A2 for a complete list of author disclosures.

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Table 1. Standardized protocol for home BP measurement (Grade D).

• Measurements should be taken with a validated electronic device.
• Choose a cuff with an appropriate bladder size matched to the size of the arm. Bladder width should be close to 40% of arm circumference and bladder length should cover 80 – 100% of arm circumference. Select the cuff size as recommended by its manufacturer.
• Cuff should be applied to the non-dominant arm unless the SBP difference between arms is >10 mmHg, in which case the arm with the highest value obtained should be used.
• The patient should be resting comfortably for 5 minutes in the seated position with back support.
• The arm should be bare and supported with the BP cuff at heart level.
• Measurement should be performed before breakfast and 2 hours after dinner, before taking medication.
• No caffeine or tobacco in the hour and no exercise 30 minutes preceding the measurement.
• Duplicate measurement should be done in the morning and in the evening for seven days (i.e., 28 measurements in total).
• Average the results excluding the first day's readings.

Table 2. Standardized protocol for ambulatory BP monitoring (Grade D).

• The appropriate sized cuff should be applied to the non-dominant arm unless the SBP difference between arms is >10 mm Hg, in which case the arm with the highest value obtained should be used.
• The device should be set to record for a duration of at least 24 hours with the measurement frequency set at 20-30 minute intervals during the day and 30-60 minutes at night.
• A patient-reported diary to define daytime (awake), night-time (sleep), activities, symptoms and medication administration is useful for study interpretation.
• Daytime and night-time should preferentially be defined using the patient's diary. Alternatively, pre-defined thresholds can be used (e.g. 8h to 22h for awake and 22h and 8h for night-time).
• The ambulatory BP monitoring report should include all of the individual BP readings (both numerically and graphically), the percentage of successful readings, the averages for each time frame (daytime, night-time, 24 hours) and the "dipping" percentage (the percentage the average BP changed from daytime to night-time).
• Criteria for a successful ambulatory BP monitoring study are:

-At least 70% of the readings are successful AND

-At least 20 daytime readings and 7 night-time readings are successful.

Table 3. Considerations in the individualization of pharmacological therapy

	Initial therapy	Second-line therapy	Notes and/or cautions
Hypertension without other compelling indications			
Diastolic hypertension with or without systolic hypertension (target BP <140/90 mmHg)	Thiazide/thiazide-like diuretics, β blockers, ACE inhibitors, ARBs, or long-acting calcium channel blockers (consider ASA and statins in selected patients). Consider initiating therapy with a combination of first-line drugs if the BP is ≥20 mmHg systolic or ≥10 mmHg diastolic above target	Combinations of first-line drugs	Not recommended for monotherapy: α blockers, β blockers in those ≥60 years of age, ACE inhibitors in black people. Hypokalemia should be avoided in those prescribed diuretics. ACE inhibitors, ARBs and direct renin inhibitors are potential teratogens, and caution is required if prescribing to women with child-bearing potential. Combination of an ACE-inhibitor with an ARB is not recommended.
Isolated systolic hypertension without other compelling indications (Target BP for age<80 is <140/90 mmHg; for age≥80: target SBP is <150 mmHg	Thiazide/thiazide-like diuretics, ARBs or long-acting dihydropyridine calcium channel blockers	Combinations of first-line drugs	Same as diastolic hypertension with or without systolic hypertension
Diabetes mellitus (target BP <130/80 mmHg)			
Diabetes mellitus	ACE inhibitors or ARBs	Addition of a dihydropyridine	A loop diuretic could be considered in

with microalbuminuria*, renal disease, cardiovascular disease or additional cardiovascular risk factors		CCB is preferred over a thiazide/thiazide-like diuretic	hypertensive chronic kidney disease patients with extracellular fluid volume overload
Diabetes mellitus not included in the above category	ACE inhibitors, ARBs, dihydropyridine CCBs or Thiazide/thiazide-like diuretics	Combination of first-line drugs. If combination with ACE inhibitor is being considered, a dihydropyridine CCB is preferable to a thiazide/thiazide-like diuretic	Normal urine microalbumin to creatinine ratio <2.0 mg/mmol
Cardiovascular disease (target BP <140/90 mmHg)			
Coronary artery disease	ACE inhibitors or ARBs; β blockers for patients with stable angina	Long-acting CCBs. When combination therapy is being used for high risk patients, an ACE inhibitor/ dihydropyridine CCB is preferred	Avoid short-acting nifedipine. Combination of an ACE-inhibitor with an ARB is specifically not recommended. Exercise caution when lowering SBP to target if DBP is ≤60 mmHg.
Recent myocardial infarction	β blockers and ACE inhibitors (ARBs if ACE inhibitor intolerant)	Long-acting CCBs if β blocker contraindicated or not effective	Non-dihydropyridine CCBs should not be used with concomitant heart failure
Heart failure	ACE inhibitors (ARBs if ACE inhibitor-intolerant) and β blockers. Aldosterone antagonists (mineralocorticoid receptor antagonists) may be added for patients with a recent cardiovascular hospitalization, acute myocardial	ACE inhibitor and ARB combined. Hydralazine/isosorbide dinitrate combination if ACE inhibitor and ARB contraindicated or not tolerated. Thiazide/thiazide-like or loop diuretics are recommended as	Titrate doses of ACE inhibitors and ARBs to those used in clinical trials. Carefully monitor potassium and renal function if combining any of ACE inhibitor, ARB and/or aldosterone antagonist.

	infarction, elevated BNP or NT-proBNP level, or NYHA Class II to IV symptoms	additive therapy. Dihydropyridine CCB can also be used.	
Left ventricular hypertrophy	ACE inhibitor, ARB, long acting CCB or thiazide/thiazide-like diuretics.	Combination of additional agents	Hydralazine and minoxidil should not be used
Past stroke or TIA	ACE inhibitor and a thiazide/thiazide-like diuretic combination.	Combination of additional agents	Treatment of hypertension should not be routinely undertaken in acute stroke unless extreme BP elevation. Combination of an ACE inhibitor with an ARB is not recommended.
Non-diabetic chronic kidney disease (target BP <140/90 mmHg)			
Non-diabetic chronic kidney disease with proteinuria†	ACE inhibitors (ARBs if ACE inhibitor-intolerant) if there is proteinuria Diuretics as additive therapy	Combinations of additional agents	Carefully monitor renal function and potassium for those on an ACE inhibitor or ARB. Combinations of an ACE-inhibitor and ARB are not recommended in patients without proteinuria
Renovascular disease	Does not affect initial treatment recommendations Renal artery stenosis should be primarily managed medically	Combinations of additional agents	Caution with ACE inhibitors or ARB if bilateral renal artery stenosis or unilateral disease with solitary kidney. Renal artery angioplasty and stenting could be considered for patients with renal artery stenosis and complicated, uncontrolled hypertension
Other conditions (target BP <140/90 mmHg)			
Peripheral arterial disease	Does not affect initial treatment recommendations	Combinations of additional agents	Avoid β blockers with severe disease
Dyslipidemia	Does not affect initial treatment recommendations	Combinations of additional agents	–

Overall vascular protection	Statin therapy for patients with 3 or more cardiovascular risk factors or atherosclerotic disease Low dose ASA in patients ≥50 years Advise on smoking cessation and use pharmacotherapy for smoking cessation if indicated	–	Caution should be exercised with the ASA recommendation if BP is not controlled.

*Microalbuminuria is defined as persistent albumin to creatinine ratio >2.0 mg/mmol.
†Proteinuria is defined as urinary protein >500 mg/24hr or albumin to creatinine ratio [ACR] >30 mg/mmol in two of three specimens.
BP blood pressure; ACE Angiotensin converting enzyme; ARB Angiotensin receptor blocker; ASA Acetylsalicylic acid; CCB Calcium channel blocker; NYHA New York Heart Association; TIA Transient ischemic attack.
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Table 4. Risk factors for hyperkalemia

Prior to advising an increase in potassium intake, the following types of patients, who are at high risk of developing hyperkalemia, should be assessed for suitability, and monitored closely: • Patients taking renin-angiotensin-aldosterone inhibitors • Patients on other drugs that can cause hyperkalemia (e.g., trimethoprim and sulfamethoxazole, amiloride, triamterene) • Chronic kidney disease (glomerular filtration rate <60 mL/min/1.73m^2) • Baseline serum potassium >4.5 mmol/L

Table 5. Clinical indications defining high risk patients as candidates for intensive management

Clinical or sub-clinical cardiovascular disease OR Chronic kidney disease (non-diabetic nephropathy, proteinuria <1 g/d, *estimated glomerular filtration rate 20-59 mL/min/1.73m^2) OR †Estimated 10-year global cardiovascular risk >15% OR Age ≥ 75 years Patients with one or more clinical indications should consent to intensive management.

*Four variable MDRD equation
†Framingham Risk Score[84]

Table 6. Generalizability of Intensive Blood Pressure Lowering: Cautions and Contraindications

Limited or No Evidence
Heart failure (ejection fraction <35%) or recent myocardial infarction (within last 3 months)
Indication for, but not currently receiving, a beta-blocker
Frail or institutionalized elderly
Inconclusive evidence
Diabetes Mellitus
Prior stroke
eGFR < 20 ml/min/1.73 m^2
Contraindications
Patient unwilling or unable to adhere to multiple medications
Standing SBP <110 mmHg
Inability to measure SBP accurately
Known secondary cause(s) of hypertension

FIGURE LEGEND

Figure 1. Hypertension diagnostic algorithm

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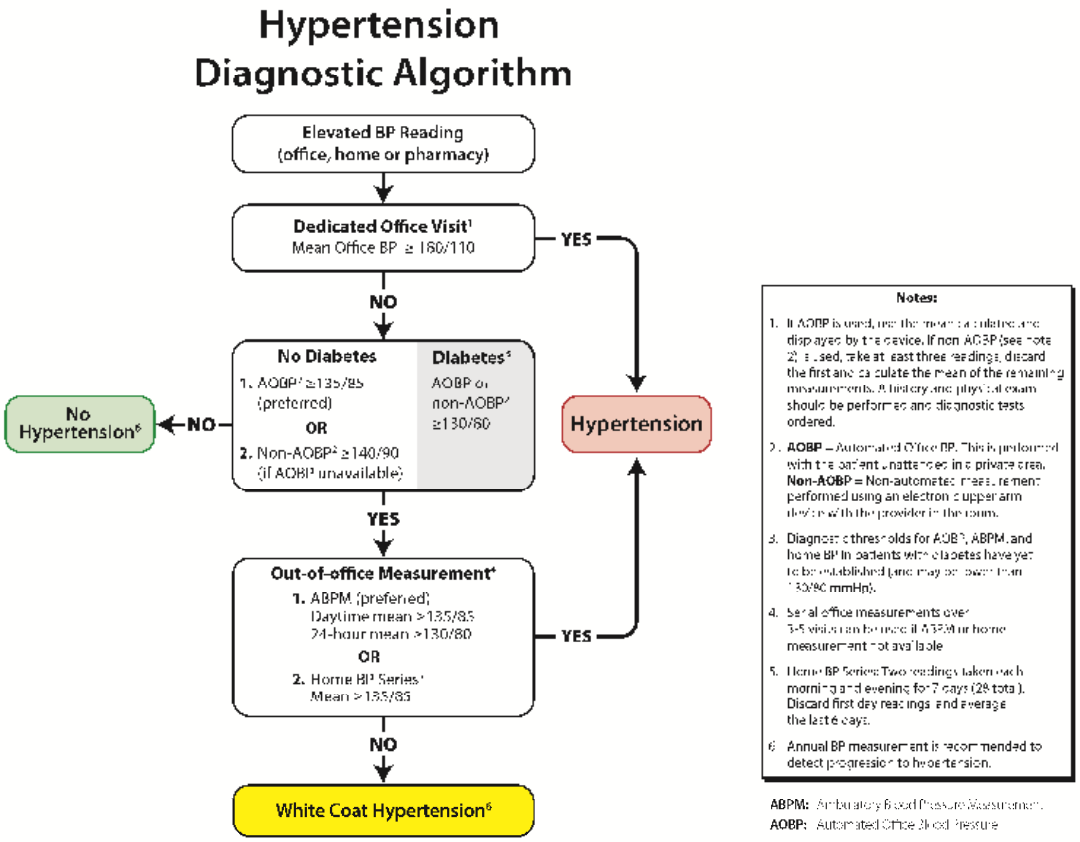
Hypertension
Diagnostic Algorithm
Elevated BP Reading
(office, home or pharmacy)
Dedicated Office Visit[1]
Mean Office BP ≥ 160/110
YES
NO
No Diabetes
1. AOBP[2] ≥135/85
(preferred)
OR
2. Non-AOBP[2] ≥140/90
(if AOBP[3] unavailable)
Diabetes[4]
AOBP or
non-AOBP[2]
≥130/80
No
Hypertension[6]
NO
Hypertension
YES
Out-of-office Measurement[4]
1. ABPM (preferred)
Daytime mean >135/85
24-hour mean >130/80
OR
2. Home BP[5] Series[1]
Mean >135/85
YES
NO
White Coat Hypertension[6]
Notes:
1. If AOBP is used, use the mean of all readings displayed by the device. If non-AOBP (see note 2) is used, take at least three readings, discard the first and calculate the mean of the remaining measurements. A history and physical exam should be performed and diagnostic tests ordered.
2. AOBP = Automated Office BP. This is performed with the patient unattended in a private area. Non-AOBP = Non-automated measurement performed using an electronic upper arm device with the provider in the room.
3. Diagnostic thresholds for AOBP, ABPM, and home BP in patients with diabetes have yet to be established (and may be lower than 130/80 mmHg).
4. Serial office measurements over 3-5 visits can be used if ABPM or home measurement not available
5. Home BP Series: Two readings taken each morning and evening for 7 days (28 total). Discard first day readings and average the last 6 days.
6. Annual BP measurement is recommended to detect progression to hypertension.
ABPM: Ambulatory Blood Pressure Measurement
AOBP: Automated Office Blood Pressure