The 2008 Canadian Hypertension Education Program recommendations for the management of hypertension: Part 2 – therapy

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OBJECTIVE: To update the evidence-based recommendations for the prevention and management of hypertension in adults.

OPTIONS AND OUTCOMES: For lifestyle and pharmacological interventions, evidence was preferentially reviewed from randomized controlled trials and systematic reviews of trials. Changes in cardiovascular morbidity and mortality were the primary outcomes of interest. However, for lifestyle interventions, blood pressure lowering was accepted as a primary outcome given the lack of long-term morbidity and mortality data in this field. Progression of kidney dysfunction was also accepted as a clinically relevant primary outcome among patients with chronic kidney disease.

EVIDENCE: A Cochrane collaboration librarian conducted an independent MEDLINE search from 2006 to August 2007 to update the 2007

recommendations. To identify additional published studies, reference lists were reviewed and experts were contacted. All relevant articles were reviewed and appraised independently by content and methodological experts using prespecified levels of evidence.

RECOMMENDATIONS: For lifestyle modifications to prevent and treat hypertension, restrict dietary sodium intake to less than 100 mmol/day (and 65 mmol/day to 100 mmol/day in hypertensive patients); perform 30 min to 60 min of aerobic exercise four to seven days per week; maintain a healthy body weight (body mass index 18.5 kg/m² to 24.9 kg/m²) and waist circumference (smaller than 102 cm for men and smaller than 88 cm for women); limit alcohol consumption to no more than 14 units per week in men or nine units per week in women; follow a diet that is reduced in saturated fat and cholesterol, and one that emphasizes fruits, vegetables and low-fat dairy products, dietary and soluble fibre, whole grains and protein from plant sources; and consider stress management in selected individuals with hypertension. For the pharmacological management of hypertension, treatment thresholds and targets should be predicated on by the patient's global atherosclerotic risk, target organ damage and comorbid

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conditions. Blood pressure should be decreased to lower than 140/90 mmHg in all patients, and to lower than 130/80 mmHg in those with diabetes mellitus or chronic kidney disease. Most patients will require more than one agent to achieve these target blood pressures. For adults without compelling indications for other agents, initial therapy should include thiazide diuretics. Other agents appropriate for first-line therapy for diastolic and/or systolic hypertension include angiotensin-converting enzyme (ACE) inhibitors (in nonblack patients), long-acting calcium channel blockers (CCBs), angiotensin receptor antagonists (ARBs) or beta-blockers (in those younger than 60 years of age). A combination of two first-line agents may also be considered for initial treatment of hypertension if systolic blood pressure is 20 mmHg above target or if diastolic blood pressure is 10 mmHg above target. Other agents appropriate for first-line therapy for isolated systolic hypertension include long-acting dihydropyridine CCBs or ARBs. In patients with angina, recent myocardial infarction or heart failure, beta-blockers and ACE inhibitors are recommended as first-line therapy; in patients with cerebrovascular disease, an ACE inhibitor/diuretic combination is preferred; in patients with proteinuric nondiabetic chronic kidney disease, ACE inhibitors are recommended; and in patients with diabetes mellitus, ACE inhibitors or ARBs (or, in patients without albuminuria, thiazides or dihydropyridine CCBs) are appropriate first-line therapies. All hypertensive patients with dyslipidemia should be treated using the thresholds, targets and agents outlined in the Canadian Cardiovascular Society position statement (recommendations for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease). Selected high-risk patients with hypertension but who do not achieve thresholds for statin therapy according to the position paper should nonetheless receive statin therapy. Once blood pressure is controlled, acetylsalicylic acid therapy should be considered.

VALIDATION: All recommendations were graded according to strength of the evidence and voted on by the 57 members of the Canadian Hypertension Education Program Evidence-Based Recommendations Task Force. All recommendations reported here achieved at least 95% consensus. These guidelines will continue to be updated annually.

Key Words: Antihypertensive drugs; Blood pressure; Guidelines; High blood pressure; Hypertension; Lifestyle interventions

Les recommandations de 2008 du Programme d'éducation canadien sur l'hypertension pour la prise en charge de l'hypertension : 2^e partie – le traitement

BUT : Mettre à jour les recommandations probantes pour la prévention et la prise en charge de l'hypertension chez les adultes.

POSSIBILITÉS ET ISSUES : Dans le cadre d'interventions pharmacologiques et touchant le mode de vie, les auteurs ont procédé à une analyse préférentielle des données tirées d'essais aléatoires et contrôlés et d'analyses systématiques d'essais. Tandis que des modifications à la morbidité et à la mortalité cardiovasculaires constituaient les principales issues d'intérêt, dans le cas des interventions touchant le mode de vie, la diminution de la tension artérielle était acceptée comme issue primaire en raison de l'absence de données à long terme sur la morbidité et la mortalité dans ce secteur. Dans le cas des patients atteints d'une néphropathie chronique, l'aggravation du dysfonctionnement rénal constituait également une issue primaire pertinente d'un point de vue clinique.

DONNÉES PROBANTES : Un bibliothécaire de Collaboration Cochrane a effectué une recherche indépendante dans la base de données MEDLINE entre 2006 et août 2007, afin de mettre les recommandations de 2007 à jour. On a également dépouillé les listes de référence et

communiqué avec des experts pour repérer d'autres études publiées. Tous les articles pertinents ont été analysés et évalués de manière indépendante par des experts du contenu et de la méthodologie, au moyen de qualités des preuves préétablies.

RECOMMANDATIONS : Les modifications au mode de vie pour prévenir ou traiter l'hypertension consistent à réduire la quantité de sel d'origine alimentaire à moins de 100 mmol/jour (et à entre 65 mmol/jour et 100 mmol/jour pour les hypertendus), à pratiquer des activités aérobiques de 30 à 60 min quatre à sept jours par semaine, à maintenir un poids santé (indice de masse corporelle de 18,5 kg/m² à 24,9 kg/m²) et un tour de taille sain (inférieur à 102 cm chez les hommes à 88 cm chez les femmes), à limiter la consommation d'alcool à 14 unités par semaine chez les hommes et à neuf unités par semaine chez les femmes, à respecter un régime alimentaire pauvre en gras saturés et en cholestérol et riche en fruits et légumes, en produits laitiers à faible teneur en matières grasses, en fibres alimentaires et solubles ainsi qu'en grains entiers et en protéines d'origine végétale, et à envisager des techniques de maîtrise du stress pour certaines personnes hypertendues. Pour ce qui est de la prise en charge pharmacologique de l'hypertension, les valeurs seuils et les valeurs cibles de traitement doivent dépendre du risque athérosclérotique global du patient, de l'atteinte des organes cibles et des pathologies comorbides. Il faut abaisser la tension artérielle à moins de 140/90 mm Hg chez tous les patients et à moins de 130/80 mm Hg chez les patients diabétiques ou atteints d'une néphropathie chronique. La plupart des patients adultes devront prendre plus d'un médicament pour parvenir aux valeurs cibles. Chez les adultes qui ne sont pas tenus de prendre d'autres agents, le traitement initial devrait inclure des diurétiques thiazidiques. D'autres médicaments conviennent au traitement de première intention de l'hypertension diastolique associée ou non à une hypertension systolique, soit les inhibiteurs de l'enzyme de conversion de l'angiotensine (ECA, sauf chez les patients noirs), les inhibiteurs calciques (IC) à action prolongée, les antagonistes des récepteurs de l'angiotensine (ARA) et les bêtabloquants (chez les personnes de moins de 60 ans). On peut également envisager deux médicaments de première intention pour le traitement initial de l'hypertension si la tension artérielle systolique dépasse la cible d'au moins 20 mm Hg ou si la tension artérielle diastolique la dépasse d'au moins 10 mm Hg. D'autres médicaments conviennent au traitement de première intention de l'hypertension systolique isolée, y compris les IC dihydropyridiniques à action prolongée ou les ARA. Aussi, chez les patients angineux, ayant récemment subi un infarctus du myocarde ou atteints d'une insuffisance cardiaque, des bêtabloquants et des inhibiteurs de l'ECA sont recommandés en première intention. Chez les patients atteints d'une maladie vasculaire cérébrale, l'association d'un inhibiteur de l'ECA et d'un diurétique est à privilégier, tandis que chez les patients atteints d'une néphropathie chronique non diabétique avec protéinurie, les inhibiteurs de l'ECA sont recommandés et chez les diabétiques, les inhibiteurs de l'ECA ou les ARA (ou, chez les patients ne présentant pas d'albuminurie, les thiazidiques ou les IC dihydropyridiniques) conviennent en première intention. Tous les patients hypertendus dyslipidémiques doivent être traités selon les seuils, les valeurs cibles et les médicaments proposés dans le document de principes de la Société canadienne de cardiologie (recommandations sur le diagnostic et le traitement de la dyslipidémie et la prévention des maladies cardiovasculaires). D'après ce document, certains patients hypertendus très vulnérables qui n'atteignent pas les seuils leur donnant droit à un traitement aux statines devraient tout de même recevoir ce traitement. Un traitement à l'acide acétylsalicylique pourra être envisagé une fois la tension artérielle stabilisée.

VALIDATION : Toutes les recommandations ont été classées selon la solidité des données probantes, et les 57 membres du groupe de travail des recommandations du Programme éducatif canadien sur l'hypertension ont exercé leur vote à leur égard. Toutes les recommandations publiées ont obtenu un consensus d'au moins 95 %. Ces lignes directrices continueront d'être mises à jour chaque année.

Hypertension is one of the most important modifiable risk factors for preventing cardiovascular disease and death (1-3). Care of the hypertensive patient is constantly evolving in response to new data published each year. To ensure that patients receive timely benefit from important new advances in hypertension research, the Canadian Hypertension Education Program (CHEP) Recommendations Task Force conducts an annual review of recently published hypertension

treatment studies. These data are translated into practical, updated, evidence-based recommendations for primary care providers on the management of adults with hypertension. In the present report, we provide the complete 2008 recommendations for lifestyle and pharmacological management of hypertension, as well as the evidence and rationale supporting all new recommendations. Summary documents of these recommendations, along with a freely downloadable slide kit,

are available on the Canadian Hypertension Society Web site (www.hypertension.ca).

For 2008, there have been several important developments, including expanding the role of combination therapy in the initial treatment of hypertension based on the recent publication of the Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation (ADVANCE) trial (4), and review of the Felodipine Event Reduction (FEVER) trial (5), the Heart Outcomes Prevention Evaluation (HOPE) (6) and the Perindopril pROtection aGainst REcurrent Stroke Study (PROGRESS) (7), as well as clarifying the optimal antihypertensive dosages for patients with heart failure. We also review findings from a post hoc analysis of the PROGRESS trial (8) evaluating the associations of achieved follow-up blood pressure levels with stroke risk.

Although we mention individual antihypertensive agents when discussing hypertension trials, the reader may assume that all drug-specific recommendations are applicable to the entire drug class in question, unless otherwise specified. Finally, while these recommendations are based on best evidence, health care providers must also use their own clinical judgement and consider patient preferences when applying these recommendations to their patients.

METHODS

A Cochrane collaboration librarian conducted a MEDLINE search using a highly sensitive search strategy for randomized trials and systematic reviews published from 2006 to August 2007. To ensure that all relevant studies were included, bibliographies of identified articles were hand-searched. (Details of search strategies and retrieved articles are available on request.)

Each subgroup, consisting of national and international hypertension experts (see Appendix), reviewed all identified articles relevant to their topic area. Members of the Canadian Diabetes Association Guidelines Committee and Canadian Society of Nephrology collaborated with CHEP subgroup members for the 2008 recommendations process. The subgroups appraised the quality of relevant studies using a standardized algorithm developed by CHEP (9). Subsequently, the central review committee, consisting of clinical epidemiologists (see Appendix), reviewed the draft recommendations from each subgroup and, in an iterative process, helped to refine and standardize all recommendations and their grading across subgroups (see Table 1).

The draft recommendations from each subgroup were then formally vetted at the 2007 consensus conference held in Quebec City, Quebec, by task force committee members, as well as members from the Canadian Diabetes Association Guidelines Committee and the Canadian Society of Nephrology. Based on the deliberations at the consensus conference, the 2008 recommendations were finalized and submitted to all 57 voting members of the CHEP Evidence-Based Recommendations Task Force for approval. Members with conflicts of interest for certain recommendations were recused from voting. As in previous years, only those recommendations approved by more than 70% of the task force were included in the final recommendations presented here.

I. Lifestyle management

Recommendations

A. Physical exercise

1. For nonhypertensive individuals (to reduce the possibility of becoming hypertensive) or for hypertensive patients (to reduce blood pressure), prescribe the accumulation of 30 min to 60 min of moderate intensity dynamic exercise (such as walking, jogging, cycling or swimming) four to seven days per week, in addition to the routine activities of daily living (grade D). Higher intensities of exercise are no 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).

TABLE 1
Grading scheme for recommendations

Grade A	Recommendations are based on randomized trials (or systematic reviews of trials) with high levels of internal validity and statistical precision, and for which the study results can be directly applied to patients because of similar clinical characteristics and the clinical relevance of the study outcomes
Grade B	Recommendations are based on randomized trials, systematic reviews, or prespecified subgroup analyses of randomized trials that have lower precision, or there is a need to extrapolate from studies because of differing populations or reporting of validated intermediate/surrogate outcomes rather than clinically important outcomes
Grade C	Recommendations from trials that have lower levels of internal validity and/or precision or report unvalidated surrogate outcomes, or results from nonrandomized observational studies
Grade D	Recommendations are based on expert opinion alone

2. Maintenance of a healthy body weight (body mass index 18.5 kg/m² to 24.9 kg/m², and waist circumference of less than 102 cm for men and less than 88 cm for women) is recommended for nonhypertensive individuals to prevent hypertension (grade C) and for hypertensive patients to reduce blood pressure (grade B). All overweight hypertensive individuals should be advised to lose weight (grade B).
3. Weight loss strategies should use a multidisciplinary approach that includes dietary education, increased physical activity and behavioural intervention (grade B).

C. Alcohol consumption

1. To reduce blood pressure, alcohol consumption should be in accordance with Canadian low-risk drinking guidelines in both normotensive and hypertensive individuals. Healthy adults should limit alcohol consumption to two drinks or less per day, and consumption should not exceed 14 standard drinks per week for men and nine standard drinks per week for women (grade B). (Note: one standard drink is considered to be 13.6 g or 17.2 mL of ethanol, or approximately 44 mL of 80 proof [40%] spirits, 355 mL of 5% beer or 148 mL 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 and low-fat dairy products, dietary and soluble fibre, whole grains, and protein from plant sources that is reduced in saturated fat and cholesterol (Dietary Approaches to Stop Hypertension [DASH] diet; Table 2) (grade B).

E. Salt intake

1. For prevention of hypertension, in addition to a well-balanced diet, a dietary sodium intake of less than 100 mmol (2300 mg) per day is recommended (grade B).
2. In hypertensive patients, dietary sodium intake should be limited to 65 mmol to 100 mmol (1495 mg to 2300 mg) per day (grade B).

F. Potassium, calcium and magnesium intake

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

TABLE 2
Dietary Approaches to Stop Hypertension (DASH) diet

Food group	Servings	Examples and notes
Grains	7–8/day	Whole wheat bread, oatmeal, popcorn
Vegetables	4–5/day	Tomatoes, potatoes, carrots, beans, peas, squash, spinach
Fruits	4–5/day	Apricots, bananas, grapes, oranges, grapefruit, melons
Low-fat or fat-free dairy foods	2–3/day	Fat-free (skim) or low-fat (1%) milk, fat-free or low-fat yogurt, fat-free or low-fat cheese
Meats, poultry, fish	2/day	Select only lean meats and trim away fat. Broil, roast or boil; no frying. Remove skin from poultry
Nuts, seeds, dry beans	4–5/week	Almonds, peanuts, walnuts, sunflower seeds, soybeans, lentils
Fats and oils	2–3/day	Soft margarines, low-fat mayonnaise, vegetable oil (olive, corn, canola or safflower)
Sweets	5/week	Maple syrup, sugar, jelly, jam, hard candy, sorbet

DASH eating plan available at <www.nhlbi.nih.gov/health/public/heart/hbp/dash/new_dash.pdf>

G. Stress management

1. In hypertensive patients in whom stress may be contributing to blood pressure elevation, 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

Lifestyle modifications are a critical part of the prevention and treatment of hypertension. Regular physical activity is independently associated with reductions in blood pressure (10), type 2 diabetes (11), cardiovascular events and all-cause mortality (12). Because these benefits of physical activity appear to be dose-related (13,14), and to be consistent with the American Heart Association (15) and American College of Sports Medicine exercise guidelines (16), CHEP has clarified that the recommended exercise prescription is in addition to the routine activities of daily living (grade D).

The remaining recommendations for lifestyle modifications are unchanged this year because there were no substantive changes in the evidence base (17,18).

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

Recommendations

1. Antihypertensive therapy should be prescribed for average diastolic blood pressure of 100 mmHg or higher (grade A) or average systolic blood pressure of 160 mmHg or higher (grade A) in patients without macrovascular target organ damage or other cardiovascular risk factors (see Tables 3 and 4 from Padwal et al, pages 455-463 in this issue of the *Journal*).
2. Antihypertensive therapy should be strongly considered if diastolic blood pressure readings average 90 mmHg or higher in the presence of macrovascular target organ damage or other independent cardiovascular risk factors (grade A).
3. Antihypertensive therapy should be strongly considered if systolic blood pressure readings average 140 mmHg or higher in the presence of macrovascular target organ damage (grade C for 140 mmHg to 160 mmHg, grade A for higher than 160 mmHg).

Background

These decision thresholds are unchanged this year because there were no substantive changes in the evidence base described in previous iterations of these guidelines (18,19).

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

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

1. Initial therapy should consist of monotherapy with a thiazide diuretic (grade A), a beta-blocker (in patients younger than 60 years of age, grade B), an angiotensin-converting enzyme (ACE) inhibitor (in nonblack patients, grade B), a long-acting calcium channel blocker (CCB) (grade B) or an angiotensin receptor blocker (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 diuretic monotherapy (grade C).
2. Additional antihypertensive drugs should be used if target blood pressure 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 diuretic or CCB with an ACE inhibitor, ARB or a beta-blocker (grade B for the combination of thiazide diuretic with 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 nondihydropyridine CCB and a beta-blocker (grade D).
3. Combination therapy using two first-line agents may also be considered as initial treatment of hypertension if systolic blood pressure is 20 mmHg above target or if diastolic blood pressure is 10 mmHg above target (grade C). However, caution should be exercised in patients in whom a substantial fall in blood pressure is more likely or more poorly tolerated (eg, elderly patients) from initial combination therapy.
4. If blood pressure is still not controlled with a combination of two or more first-line agents, or if there are adverse effects, other antihypertensive drugs may be added (grade D).
5. Possible reasons for poor response to therapy (Table 3) should be considered (grade D).
6. Alpha-blockers are not recommended as first-line agents for uncomplicated hypertension (grade A), beta-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.

B. Recommendations for individuals with isolated systolic hypertension

1. Initial therapy should be monotherapy with a thiazide 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 diuretic monotherapy (grade C).
2. Additional antihypertensive drugs should be used if target blood pressure levels are not achieved with standard-dose monotherapy (grade B). Add-on drugs should be chosen from first-line choices (grade D).
3. If blood pressure is still not controlled with a combination of two or more first-line agents, or if there are adverse effects,

other classes of drugs (such as alpha-blockers, ACE inhibitors, centrally acting agents or nondihydropyridine CCBs) may be added or substituted (grade D).

4. Possible reasons for poor response to therapy (Table 3) should be considered (grade D).
5. Alpha-blockers are not recommended as first-line agents for uncomplicated isolated systolic hypertension (grade A), and beta-blockers are not recommended as first-line therapy for isolated systolic hypertension in patients 60 years of age or older (grade A). However, both agents may be used in patients with certain comorbid conditions or in combination therapy.

Background

There is a large and compelling body of literature demonstrating that antihypertensive drug therapy is associated with a 20% to 25% reduction in cardiovascular events and a 10% reduction in mortality (20). The majority of these studies were based on step-up titration schemes, in which a single agent was initiated and doses were titrated upward or other antihypertensive agents were added until target blood pressure was achieved. These studies form the foundation for the grades A and B monotherapy recommendations, and represent the primary strategy for initiating antihypertensive drug therapy. However, because many patients require more than one drug to achieve blood pressure targets, hypertension trials are now evaluating the safety and efficacy of initial combination therapy on reduction of cardiovascular end points. On review of these trials, CHEP included a grade C recommendation supporting combination therapy for initial treatment. In the FEVER trial (5), 9711 hypertensive patients from China 50 to 79 years of age were initiated on low-dose hydrochlorothiazide and then randomly assigned to additional low-dose felodipine or placebo. After a mean follow-up of 3.3 years, those assigned to combination felodipine plus hydrochlorothiazide had lower blood pressure and a significantly lower risk of fatal or nonfatal stroke (hazard ratio [HR] 0.73; 95% CI 0.60 to 0.89), cardiovascular events (HR 0.73; 95% CI 0.61 to 0.86) and total mortality (HR 0.69; 95% CI 0.54 to 0.89). In addition, the PROGRESS trial (7) demonstrated a greater blood pressure lowering effect and a significant reduction in stroke incidence (RR 0.57; 95% CI 0.46 to 0.70; $P < 0.001$) in patients allocated to combination therapy (indapamide plus perindopril) compared with placebo among 6105 patients with a history of stroke or transient ischemic attack. However, single drug therapy was not associated with a reduction in stroke. The results from PROGRESS need to be interpreted with caution because allocation to combination therapy compared with monotherapy was determined by the physician rather than through random assignment. In the blood pressure-lowering arm of the ADVANCE trial (4), 11,140 patients aged 55 years or older with type 2 diabetes and a history of major vascular disease or vascular risk factors were randomly assigned to perindopril plus indapamide versus placebo, in addition to their current antihypertensive therapy. After a mean follow-up of 4.3 years, combination therapy was associated with a 5.6/2.2 mmHg greater reduction in blood pressure compared with placebo. However, there were no significant differences in the macrovascular or microvascular primary end points between combination therapy and placebo. Although the HR favoured perindopril plus indapamide therapy when these major end points were combined, the CI included 1.0, indicating that no difference between the treatment groups was still possible. In the secondary end point analysis, however, combination therapy was associated with a significant reduction in cardiovascular death (HR 0.82; 95% CI 0.68 to 0.98; $P = 0.03$) and total mortality (HR 0.86; 95% CI 0.75 to 0.98; $P = 0.03$) compared with placebo. This study was given a grade C rating because the benefits of combination therapy were largely found in the secondary end point evaluation, where multiple secondary end points were tested, and because of the need to extrapolate from a diabetic population. Despite the limitations of these studies, the findings collectively support a greater blood pressure-lowering effect with combination

TABLE 3
Possible reasons for poor response to antihypertensive therapy

Noncompliance
Dietary
Medication
Associated conditions
Obesity
Cigarette smoking
Excessive alcohol consumption
Sleep apnea
Chronic pain and/or mental illness
Drug interactions
Nonsteroidal anti-inflammatory drugs (including cyclo-oxygenase-2 inhibitors)
Oral contraceptives
Corticosteroids and anabolic steroids
Sympathomimetics and decongestants
Cocaine
Amphetamines
Erythropoietin
Cyclosporine, tacrolimus
Licorice
Over-the-counter dietary supplements (eg, ephedra, ma huang, bitter orange)
Suboptimal treatment regimens
Dosage too low
Inappropriate combinations of antihypertensive agents
Volume overload
Excessive salt intake
Renal sodium retention (pseudotolerance)
Secondary hypertension
Renal insufficiency
Renovascular disease
Primary hyperaldosteronism
Thyroid disease
Pheochromocytoma and other rare endocrine causes

Note that causes of pseudo-resistance (such as white coat hypertension or pseudohypertension in elderly patients) should be ruled out first. Adapted from reference 26

therapy compared with monotherapy and a reduction in cardiovascular end points. Given the significantly greater blood pressure reductions associated with combination therapy, CHEP added the proviso that a combination of two first-line agents should be used in patients with a significant elevation in blood pressure, and caution should be exercised in patients in whom a substantial fall in blood pressure is more likely to occur or is more poorly tolerated (eg, elderly patients).

The remaining recommendations are unchanged this year and the supporting evidence is discussed in previous recommendations documents (19,21).

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

1. Statin therapy is recommended in hypertensive patients with three or more cardiovascular risk factors as defined in Table 4 (grade A in patients older than 40 years) or with established atherosclerotic disease (grade A regardless of age).
2. Strong consideration should be given to the addition of low-dose acetylsalicylic acid therapy in hypertensive patients (grade A in patients older than 50 years). Caution should be exercised if blood pressure is not controlled (grade C).

TABLE 4
Cardiovascular risk factors for consideration of statin therapy in nondyslipidemic patients with hypertension

Male sex
Age ≥ 55 years
Left ventricular hypertrophy
Other electrocardiogram abnormalities: left bundle branch block, left ventricular strain pattern, abnormal Q waves or ST-T changes compatible with ischemic heart disease
Peripheral arterial disease
Previous stroke or transient ischemic attack
Microalbuminuria or proteinuria
Diabetes mellitus
Smoking
Family history of premature cardiovascular disease
Total cholesterol to high-density lipoprotein cholesterol ratio ≥ 6

If hypertensive patients have 3 or more of these risk factors, statins should be considered. Derived from reference 28

Background

Because there has not been a significant change in the evidence base, these recommendations are unchanged (21).

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

1. The systolic blood pressure treatment goal is lower than 140 mmHg (grade C). The diastolic blood pressure treatment goal is lower than 90 mmHg (grade A).

Background

Because there has not been a substantive change in the evidence base, these recommendations are unchanged from previous recommendations (19).

VI. Treatment of hypertension in association with ischemic heart disease

A. Recommendations for hypertensive patients with coronary artery disease

1. An ACE inhibitor is recommended for most patients with hypertension and documented coronary artery disease (grade A).
2. For patients with stable angina, beta-blockers are preferred as initial therapy (grade B). Long-acting CCBs may also be used (grade B).
3. Short-acting nifedipine should not be used (grade D).

B. Recommendations for patients with hypertension who have had a recent ST-elevation myocardial infarction or non-ST segment elevation myocardial infarction

1. Initial therapy should include both a beta-blocker and an ACE inhibitor (grade A). An ARB may be used if the patient is intolerant of an ACE inhibitor (grade A in patients with left ventricular systolic dysfunction).
2. Long-acting CCBs may be used in postmyocardial infarction patients when beta-blockers are contraindicated or not effective. Nondihydropyridine CCBs should not be used when there is heart failure as evidenced by pulmonary congestion on examination or radiograph (grade D).

Background

Because there has not been a substantial change in the evidence base this year, these recommendations remain unchanged from previous

iterations (19). Please also note that while ACE inhibitors reduce cardiovascular events among most patients with coronary artery disease, these benefits do not appear to extend to coronary artery disease patients with low cardiovascular risk (ie, those with normal ejection fraction, adequate coronary revascularization and well-controlled atherosclerotic risk factors). It should also be noted that CHEP guidelines recommend that blood pressure be lowered to 140/90 mmHg or lower, but they do not specify aggressively lowering blood pressure in patients with ischemic heart disease because of the unanswered question about whether excess lowering of blood pressure in patients with coronary artery disease accentuates myocardial ischemia. This position is similar to the one taken by the American Heart Association and American College of Cardiology in recent recommendations (22).

VII. Treatment of hypertension in association with heart failure

1. 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).
2. In patients with systolic dysfunction, ACE inhibitors (grade A) and beta-blockers (grade A) are recommended for initial therapy. Aldosterone antagonists (grade B) are also recommended for patients with New York Heart Association functional class III or IV symptoms of heart failure or following myocardial infarction. Other diuretics are recommended as additional therapy if needed (grade B for thiazide diuretics for blood pressure control and grade D for loop diuretics for volume control). Beyond considerations of blood pressure control, doses of ACE inhibitors or ARBs should be titrated to those found to be effective in trials unless adverse effects are manifest (grade B).
3. An ARB is recommended if ACE inhibitors are not tolerated (grade A).
4. A combination of hydralazine and isosorbide dinitrate is recommended if ACE inhibitors and ARBs are contraindicated or not tolerated (grade B).
5. For hypertensive patients whose blood pressure 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 ACE inhibitor and ARB due to potential adverse effects such as hypotension, hyperkalemia and worsening renal function (grade C). Additional therapies may also include long-acting dihydropyridine CCBs (grade C).

Background

ACE inhibitors and ARBs are associated with significant reductions in cardiovascular events among patients with heart failure (23,24). Consistent with the Canadian Cardiovascular Society recommendations on heart failure (25), CHEP has clarified that the dosages of ACE inhibitors and ARBs should be titrated to those dosages found to be effective in the clinical trials unless adverse effects arise. The remaining recommendations are unchanged from previous iterations (19,21).

VIII. Treatment of hypertension in association with cerebrovascular disease

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. Caution is indicated when deciding whether to lower blood pressure in the acute stroke situation; pharmacological agents

and routes of administration should be chosen to avoid precipitous falls in blood pressure (grade D).

- Following the acute phase of a stroke, patients should have their blood pressure chronically controlled to a target of lower than 140/90 mmHg (grade C).
- Treatment with an ACE inhibitor plus diuretic combination is preferred (grade B).

Background

Although antihypertensive therapy is well established in the secondary prevention of stroke, it is unclear whether lowering blood pressure beyond 140/90 mmHg would provide additional benefits. Benefits of aggressive blood pressure lowering would have to be weighed against the risk of inducing cerebral hypotension and iatrogenic stroke. In a post hoc analysis of the PROGRESS trial (8), investigators determined the effects of achieved follow-up blood pressure levels on stroke risk among 6105 normotensive and hypertensive individuals with previous stroke or transient ischemic attack. Stroke incidence declined with no evidence of a J curve, with progressively lower achieved follow-up systolic blood pressure throughout the range of blood pressures (112 mmHg to 168 mmHg). While this analysis reassures that lowering blood pressure in a heterogeneous stroke population may not precipitate stroke in the recommended target of lower than 140/90 mmHg, optimal blood pressure levels cannot be determined until data from randomized trials are available. The remaining recommendations are unchanged from 2007 (21).

IX. Treatment of hypertension in association with left ventricular hypertrophy

- Hypertensive patients with left ventricular hypertrophy should be treated with antihypertensive therapy to decrease the rate of subsequent cardiovascular events (grade C).
- 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 diuretics. Direct arterial vasodilators such as hydralazine or minoxidil should not be used.

Background

These recommendations are unchanged from 2007 (21).

X. Treatment of hypertension in association with nondiabetic chronic kidney disease

- For patients with nondiabetic chronic kidney disease, target blood pressure is lower than 130/80 mmHg (grade C).
- For patients with hypertension and proteinuric chronic kidney disease (urinary protein greater than 500 mg/24 h or albumin to creatinine ratio [ACR] greater than 30 mg/mmol), initial therapy should consist of an ACE inhibitor (grade A) or an ARB if there is intolerance to ACE inhibitors (grade D).
- Thiazide 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).
- In most cases, combination therapy with other antihypertensive agents may be needed to reach target blood pressure (grade D).

Background

Because there has not been a substantial change to the evidence base in this area, the above recommendations remain unchanged from previous years (21,26).

XI. Treatment of hypertension in association with renovascular disease

- Renovascular hypertension should be treated in the same manner as hypertension without compelling indications, except for caution in using ACE inhibitors or ARBs due to the risk of acute renal failure in bilateral disease or unilateral disease with a solitary kidney (grade D).
- Close follow-up and early intervention (angioplasty and stenting or surgery) should be considered for patients with uncontrolled hypertension despite therapy with three or more drugs, deteriorating kidney function, bilateral atherosclerotic renal artery lesions (or tight atherosclerotic stenosis in a single kidney) or recurrent episodes of flash pulmonary edema (grade D).

Background

Because there has not been a substantial change in the evidence base, these recommendations are unchanged this year (19).

XII. Treatment of hypertension in association with diabetes mellitus

- Patients with diabetes mellitus should be treated to attain systolic blood pressure lower than 130 mmHg (grade C) and diastolic blood pressure lower than 80 mmHg (grade A). (These target blood pressure levels are the same as the blood pressure treatment thresholds.)
- For patients with diabetes and normal urinary albumin excretion (ACR lower than 2.0 mg/mmol in men and lower than 2.8 mg/mmol in women) and without chronic kidney disease, with blood pressure 130/80 mmHg or higher despite lifestyle interventions, any of an ACE inhibitor (grade A for patients 55 years or older, grade B for patients younger than 55 years), ARB (grade A for patients with left ventricular hypertrophy and age of 55 years or older, grade B for patients without left ventricular hypertrophy irrespective of age), a dihydropyridine CCB (grade A for patients 55 years of age or older, grade B for patients younger than 55 years) or a thiazide diuretic (grade A for patients 55 years of age or older, grade B for patients younger than 55 years of age) is recommended, with special consideration to the ACE inhibitor and ARB, given their additional renal benefits. If these drugs are contraindicated or cannot be tolerated, a cardioselective beta-blocker (grade B) or nondihydropyridine CCB (grade B) may be substituted. Additional antihypertensive drugs should be used if target blood pressure is not achieved with standard-dose monotherapy (grade B). Add-on drugs should be chosen from first-line choices.
- For patients with diabetes and albuminuria (persistent ACR greater than 2.0 mg/mmol in men and greater than 2.8 mg/mmol in women), an ACE inhibitor or an ARB is recommended as initial therapy (grade A). If blood pressure remains 130/80 mmHg or higher despite lifestyle interventions and the use of an ACE inhibitor or ARB, additional antihypertensive drugs should be used to obtain target blood pressure.
- For patients with diabetes and a normal urinary albumin excretion rate (ACR lower than 2.0 mg/mmol in men and lower than 2.8 mg/mmol in women) with no chronic kidney disease and with isolated systolic hypertension, a long-acting dihydropyridine CCB (grade C) is an alternative initial choice to an ACE inhibitor (grade B), ARB (grade B) or a thiazide diuretic (grade C).
- Alpha-blockers are not recommended as first-line agents for the treatment of hypertension in patients with diabetes (grade A).

TABLE 5
Strategies to improve patient adherence

Assist your patient to adhere by:

- tailoring pill taking to fit patients' daily habits (grade D);
- simplifying medication regimens to once-daily dosing;
- replacing two antihypertensive agents with a fixed-dose combination (when available and appropriate), provided it is the same combination the patient is already taking (grade D); and
- using unit-of-use packaging (of several medications to be taken together) (grade D).

Assist your patient in getting more involved in their treatment by:

- encouraging greater patient responsibility/autonomy in monitoring their blood pressure and adjusting their prescriptions (grade C); and
- educating patients and patients' families about their disease or treatment regimens (grade C).

Improve your management in the office and beyond by:

- assessing adherence to pharmacological and nonpharmacological therapy at every visit (grade D);
- encouraging adherence with therapy by out-of-office contact (either by phone or mail), particularly over the first three months of therapy (grade D);
- coordinating with work-site health care givers to improve monitoring of adherence with pharmacological and lifestyle modification prescriptions (grade D); and
- using electronic medication compliance aids (grade D).

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TABLE 6
Treatment recommendations for patients with hyperaldosteronism

- Treatment of confirmed unilateral aldosterone-producing adenoma (APA) includes surgical removal by laparoscopic adrenalectomy.
- Patients should be treated for 8–10 weeks before surgery to correct metabolic abnormalities and control blood pressure.
- For primary aldosteronism patients with adrenal hyperplasia, bilateral adenoma or increased risk of perioperative complications, treatment is medical.
- Medical treatment should be initiated with spironolactone 25 mg – 400 mg per day (usual doses are 100 mg – 200 mg). For those intolerant to spironolactone, amiloride 10 mg – 20 mg per day is an alternative. Addition of thiazide diuretics, beta-blockers and/or calcium channel blockers may be useful to control blood pressure.
- Because many APA patients will remain hypertensive following the surgical removal of an APA, these patients should be followed and, if necessary, treated according to the usual guidelines for nonendocrine hypertension.

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Background

This year, there are no changes to the recommendations for patients with diabetes (21,26). The ADVANCE trial (4) is using a 2×2 factorial design to test the effects of blood pressure lowering with perindopril plus indapamide and intensive glucose control using a sulphonylurea on micro- and macrovascular complications in patients with type 2 diabetes. Full assessment of this trial will be considered pending the publication of the intensive glucose control arm to assess for a possible interaction between the two treatment strategies (blood pressure control and intensive glucose control) on risk for developing micro- and macrovascular complications.

TABLE 7
Treatment recommendations for patients with pheochromocytoma

- Alpha-blockers (prazosin, doxazosin and phenoxybenzamine) should be used as first-line agents in suspected pheochromocytoma. Alpha methyl-dopa or clonidine may also be used.
- Treatment of benign pheochromocytoma should be surgical resection. The following issues should be considered:
 - until surgery is performed, the use of beta-blockers should be avoided, unless arrhythmias are present and adequate alpha blockade has been achieved;
 - surgical resection should be carefully planned in advance with involvement of a team of surgical, medical, intensivist and anesthesia consultants who have experience in the management of patients with pheochromocytoma;
 - laparoscopic surgery should be considered before open surgery for resection of pheochromocytoma, except for very large tumours;
 - administration of phenoxybenzamine (10 mg – 20 mg two to three times daily) for 10–14 days, prazosin (1 mg – 3 mg two to three times daily) or doxazosin (2 mg – 4 mg two to three times daily) is indicated for patients with severe paroxysmal or sustained hypertension;
 - the tyrosine hydroxylase inhibitor metyrosine (0.25 g – 1 g four times daily) should also be considered;
 - immediately before surgery, administration of intravenous fluids should be considered to ensure adequate volume expansion to avoid shock after tumour removal;
 - for hypertensive crises before/during surgery, phentolamine hydrochloride should be readily available and, if necessary, administered intravenously; and
 - intravenous propranolol should be used for treatment of arrhythmias.
- For patients with pheochromocytoma diagnosed during early pregnancy, if a decision is made to terminate the pregnancy, this should be carried out under alpha and beta blockade (as above), followed immediately by tumour resection. In late pregnancy, alpha and beta blockade followed by elective cesarean section and immediate tumor resection are recommended.
- For patients with inoperable or metastatic malignant pheochromocytoma, blood pressure control and adrenergic symptoms may be controlled with alpha adrenergic blockade (phenoxybenzamine, prazosin, doxazosin) plus beta blockade and/or tyrosine hydroxylase inhibition with metyrosine. A combination of cyclophosphamide, vincristine and dacarbazine may be used for chemotherapy or metastatic pheochromocytoma. Treatment with high-dose iodine-131 metaiodobenzylguanidine induces only a moderate response, but it may help control blood pressure.

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XIII. Concordance strategies for patients

1. Adherence to an antihypertensive prescription can be improved by a multipronged approach, as outlined in Table 5.

Background

Because there has been no substantive change in the evidence base this past year, the recommendations for this section are unchanged (27).

XIV. Treatment of secondary hypertension due to endocrine causes

1. Treatment of hyperaldosteronism and pheochromocytoma are outlined in Tables 6 and 7.

Background

Because there has been no substantive change in the evidence base this past year, the recommendations for this section are unchanged.

TABLE 8
Considerations in the individualization of antihypertensive therapy

	Initial therapy	Second-line therapy	Notes and/or cautions
Hypertension without other compelling indications			
Diastolic $\pm$ systolic hypertension	Thiazide diuretics, beta-blockers, ACE inhibitors, ARBs or long-acting CCBs (consider ASA and statins in selected patients)	Combinations of first-line drugs	Beta-blockers are not recommended as initial therapy in those over 60 years of age. Hypokalemia should be avoided in those who are prescribed diuretics as monotherapy. ACE inhibitors are not recommended as initial therapy in black patients. ACE inhibitors and ARBs are teratogenic, and marked caution is required if prescribing to women of child-bearing potential
Isolated systolic hypertension	Thiazide diuretics, long-acting dihydropyridine CCBs or ARBs	Combinations of first-line drugs	Same as diastolic $\pm$ systolic hypertension
Diabetes mellitus			
Diabetes mellitus with albuminuria*	ACE inhibitors or ARBs	Combinations of first-line drugs	If the serum creatinine level is >150 mmol/L, a loop diuretic should be used as a replacement for low-dose thiazide diuretics if volume control is required
Diabetes mellitus without albuminuria*	ACEI inhibitors, ARBs, dihydropyridine CCBs or thiazide diuretics	Combination of first-line drugs or, if first-line agents are not tolerated, addition of cardioselective beta-blockers and/or long-acting nondihydropyridine CCBs	Albumin to creatinine ratio <2.0 mg/mmol in men and <2.8 mg/mmol in women
Cardiovascular and cerebrovascular disease			
Coronary artery disease	ACE inhibitors except in low-risk revascularized patients; beta-blockers in patients with angina	Long-acting CCBs	Avoid short-acting nifedipine
Prior myocardial infarction	Beta-blockers and ACE inhibitors (ARBs if ACE inhibitor-intolerant)	Long-acting CCBs	
Heart failure	ACE inhibitors (ARBs if ACE inhibitor-intolerant) and beta-blockers. Spironolactone in patients with NYHA class III or IV symptoms	ARBs or hydralazine/isosorbide dinitrate (thiazide or loop diuretics as additive therapy)	Avoid nondihydropyridine CCBs (diltiazem, verapamil). Monitor potassium and renal function if combining an ACE inhibitor and ARB
Left ventricular hypertrophy	ACE inhibitors, ARBs, long-acting CCBs, thiazide diuretics		Avoid hydralazine and minoxidil
Past cerebrovascular accident or transient ischemic attack	ACE inhibitor/diuretic combinations		This does not apply to acute stroke. Blood pressure reduction reduces recurrent cerebrovascular events in patients with stable past cerebrovascular disease
Nondiabetic chronic kidney disease			
Nondiabetic chronic kidney disease with proteinuria†	ACE inhibitors (ARBs if ACE inhibitor-intolerant), diuretics as additive therapy	Combinations of additional agents	Avoid ACE inhibitors or ARBs if bilateral renal artery stenosis or unilateral disease with solitary kidney. Patients placed on an ACE inhibitor or an ARB should have their serum creatinine and potassium carefully monitored
Renovascular disease	Similar to diastolic $\pm$ systolic hypertension without compelling indications for other medications		Avoid ACE inhibitors or ARBs if bilateral renal artery stenosis or unilateral disease with solitary kidney
Other conditions			
Peripheral arterial disease	Does not affect initial treatment recommendations	Does not affect initial treatment recommendations	Avoid beta-blockers in patients with severe disease
Dyslipidemia	Does not affect initial treatment recommendations	Does not affect initial treatment recommendations	
Global vascular protection	Statin therapy for patients with 3 or more cardiovascular risk factors or atherosclerotic disease. Low-dose ASA in patients with controlled blood pressure		Caution should be exercised if blood pressure is not controlled

*Albuminuria is defined as persistent albumin to creatinine ratio >2.0 mg/mmol in men and >2.8 mg/mmol in women; †Proteinuria is defined as urinary protein >500 mg/24 h or albumin to creatinine ratio >30 mg/mmol. ACE Angiotensin-converting enzyme; ARB Angiotensin receptor blocker; ASA Acetylsalicylic acid; NYHA New York Heart Association. Reproduced with permission of the Canadian Hypertension Education Program

FUTURE DIRECTIONS

The present paper represents the ninth iteration of the annually updated CHEP recommendations for the management of hypertension. A summary of the considerations for selecting antihypertensive therapy is presented in Table 8. We will continue to conduct yearly systematic reviews of clinical trial evidence to annually update our recommendations for therapy.

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APPENDIX

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