The 2010 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 treatment of hypertension in adults for 2010.

OPTIONS AND OUTCOMES: For lifestyle and pharmacological interventions, randomized trials and systematic reviews of trials were preferentially reviewed. 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 general lack of long-term morbidity and mortality data in this field. Progressive renal impairment 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 2008 to August 2009 to update the 2009 recommendations. To identify additional studies, reference lists were reviewed and experts were contacted. All relevant articles were reviewed and appraised independently by both content and methodological experts using prespecified levels of evidence.

RECOMMENDATIONS: For lifestyle modifications to prevent and treat hypertension, restrict dietary sodium to 1500 mg (65 mmol) per day in adults 50 years of age or younger, to 1300 mg (57 mmol) per day in adults 51 to 70 years of age, and to 1200 mg (52 mmol) per day in adults older than 70 years of age; perform 30 min to 60 min of moderate aerobic exercise four to seven days per week; maintain a healthy body weight (body mass index 18.5 kg/m^2 to 24.9 kg/m^2) and waist circumference (less than 102 cm for men and less than 88 cm for women); limit alcohol consumption to no more than 14 standard drinks per week for men or nine standard drinks per week for women; follow a diet that emphasizes fruits, vegetables and low-fat dairy products, dietary and soluble fibre, whole grains and protein from plant sources, and that is low in saturated fat and cholesterol; and consider stress management in selected individuals with hypertension.

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For the pharmacological management of hypertension, treatment thresholds and targets should be predicated on the patient's global atherosclerotic risk, target organ damage and comorbid conditions. Blood pressure should be decreased to less than 140/90 mmHg in all patients, and to less than 130/80 mmHg in patients with diabetes mellitus or chronic kidney disease. Most patients will require more than one agent to achieve these target blood pressures. Antihypertensive therapy should be considered in all adult patients regardless of age (caution should be exercised in elderly patients who are frail). For adults without compelling indications for other agents, considerations for initial therapy should include thiazide diuretics, angiotensin-converting enzyme (ACE) inhibitors (in patients who are not black), long-acting calcium channel blockers (CCBs), angiotensin receptor blockers (ARBs) or beta-blockers (in those younger than 60 years of age). A combination of 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. The combination of ACE inhibitors and ARBs should not be used, unless compelling indications are present to suggest consideration of dual therapy.

Agents appropriate for first-line therapy for isolated systolic hypertension include thiazide diuretics, long-acting dihydropyridine CCBs or ARBs. In patients with coronary artery disease, ACE inhibitors, ARBs or beta-blockers 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 or ARBs (if intolerant to 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. In selected high-risk patients in whom combination therapy is being considered, an ACE inhibitor plus a long-acting dihydropyridine CCB is preferable to an ACE inhibitor plus a thiazide diuretic. All hypertensive patients with dyslipidemia should be treated using the thresholds, targets and agents outlined in the Canadian lipid treatment guidelines. Selected patients with hypertension who do not achieve thresholds for statin therapy, but who are otherwise at high risk for cardiovascular events, should nonetheless receive statin therapy. Once blood pressure is controlled, low-dose acetylsalicylic acid therapy should be considered.

VALIDATION: All recommendations were graded according to the strength of the evidence and voted on by the 63 members of the Canadian Hypertension Education Program Evidence-Based Recommendations Task Force. All recommendations reported here achieved at least 80% consensus. These guidelines will continue to be updated annually.

SPONSORS: The Canadian Hypertension Education Program process is sponsored by the Canadian Hypertension Society, Blood Pressure Canada, the Public Health Agency of Canada, the College of Family Physicians of Canada, the Canadian Pharmacists Association, the Canadian Council of Cardiovascular Nurses, and the Heart and Stroke Foundation of Canada.

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

Les recommandations de 2010 du Programme éducatif canadien sur l'hypertension pour la prise en charge de l'hypertension : Partie 2 – le traitement

OBJECTIF : Mettre à jour les recommandations probantes pour la prévention et la prise en charge de l'hypertension chez les adultes en 2010.

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 insuffisance rénale chronique, l'aggravation du dysfonctionnement rénal constituait également une issue primaire pertinente sur le plan clinique.

DONNÉES PROBANTES : Un bibliothécaire de Collaboration Cochrane a effectué une recherche indépendante dans la base de données MEDLINE entre 2008 et août 2009 afin de mettre les recommandations de 2009 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 1 500 mg (65 mmol) par jour chez les adultes de 50 ans et moins, à 1 300 mg (57 mmol) par jour chez les adultes de 51 à 70 ans et à 1 200 mg (52 mmol) par jour chez ceux de plus de 70 ans, à pratiquer de 30 à 60 minutes d'exercice aérobique modéré de quatre à sept jours par semaine, à maintenir un poids santé (indice de masse corporelle de 18,5 kg/m^2 à 24,9 kg/m^2) et un tour de taille sain (inférieur à 102 cm chez les hommes et 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 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 athéroscléreux global du patient, de l'atteinte des organes cibles et des pathologies comorbides. Il faut abaisser la tension artérielle à moins de 140/90 mmHg chez tous les patients et à moins de 130/80 mmHg chez les patients diabétiques ou atteints d'une insuffisance rénale chronique. La plupart des patients devront prendre plus d'un médicament pour parvenir aux valeurs cibles. Il faut envisager la prescription d'antihypertensifs chez tous les patients adultes, quel que soit leur âge (en faisant preuve de prudence chez les patients âgés fragiles). Dans le cas des adultes chez qui il n'y pas d'indication impérieuse d'administrer d'autres médicaments, il faudrait envisager comme traitement initial des diurétiques thiazidiques, des inhibiteurs de l'enzyme de conversion de l'angiotensine (ECA, sauf chez les patients noirs), des inhibiteurs calciques (IC) à action prolongée, des antagonistes des récepteurs de l'angiotensine (ARA) ou des bétabloquants (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 mmHg ou si la tension artérielle diastolique la dépasse de 10 mmHg. Il faut éviter d'associer des inhibiteurs de l'ECA à des ARA, à moins de motifs probants incitent à envisager une bithérapie.

Les médicaments qui conviennent au traitement de première intention de l'hypertension systolique isolée sont les IC dihydropyridines à action prolongée ou les ARA. Chez les patients ayant une coronaropathie, les inhibiteurs de l'ECA, les ARA ou les bêta-bloquants sont recommandés en première intention, tandis que chez ceux atteints d'une maladie vasculaire cérébrale, l'association d'un inhibiteur de l'ECA et d'un diurétique est à privilégier. Chez les patients atteints d'une insuffisance rénale chronique non diabétique avec protéinurie, les inhibiteurs de l'ECA ou les ARA (en cas d'intolérance aux 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 dihydropyridines) conviennent en première intention. Chez certains patients très vulnérables pour qui une polythérapie est envisagée, un inhibiteur de l'ECA associé à un IC dihydropyridine à action prolongée est préférable à un inhibiteur de l'ECA associé à un diurétique thiazidique. Tous les patients hypertendus dyslipidémiques doivent être traités selon les seuils, les valeurs cibles et les médicaments proposés dans les lignes directrices canadiennes sur le traitement de la dyslipidémie. Certains patients hypertendus qui n'atteignent pas les seuils justifiant un traitement aux statines mais néanmoins très vulnérables à des événements cardiovasculaires devraient tout de même recevoir ce traitement. Une fois la tension artérielle stabilisée, un traitement à l'acide acétylsalicylique à faible dose pourra être envisagé.

VALIDATION : Toutes les recommandations sont classées selon la solidité des données probantes, et les 63 membres du groupe de travail des recommandations probantes du Programme éducatif canadien sur l'hypertension ont exercé leur vote à leur égard. Toutes les recommandations ont obtenu un consensus d'au moins 80 %. Les présentes lignes directrices continueront d'être mises à jour chaque année.

COMMANDITAIRES : Le processus du Programme éducatif canadien sur l'hypertension est commandité par la Société canadienne d'hypertension artérielle, Pression artérielle Canada, l'Agence de la santé publique du Canada, Le Collège des médecins de famille du Canada, l'Association des pharmaciens du Canada, le Conseil canadien des infirmères(iers) en nursing cardiovasculaire et la Fondation des maladies du cœur du Canada.

Worldwide, 7.6 million premature deaths each year and 92 million disability-adjusted life years are attributed to high blood pressure (1). Overall, 54% of strokes and 47% of coronary artery diseases worldwide are attributable to high blood pressure (1). High blood pressure affects one in five Canadian adults and the majority of these will require pharmacological therapy to control their blood pressure (2,3). Each year, the Canadian Hypertension Education Program (CHEP) Recommendations Task Force reviews hypertension treatment studies in an effort to alert primary care providers of new clinical advances in the management of hypertension.

This year, four landmark clinical trials inform evidence-based decision making and expand the range of options for patients with hypertension. These trials are the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) (4), the Telmisartan Randomised Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRANSCEND) (5), the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial (6) and the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial (7). Evidence has also evolved in the area of single-pill combination strategies to improve adherence and salt intake targets to prevent and treat hypertension (8,9).

The present scientific report outlines the complete 2010 recommendations for the 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). 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 stated. 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 for 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 2008 to August 2009. To ensure that all relevant studies were included, bibliographies of identified articles were manually 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 Stroke Network, the Canadian Diabetes Association Guidelines Committee and the Canadian Society of Nephrology collaborated with CHEP subgroup members for the 2010 recommendations process. The subgroups appraised the quality of relevant studies using a standardized algorithm developed by CHEP (10). Subsequently, the central review committee comprised of clinical epidemiologists reviewed draft recommendations from each subgroup and, in an iterative process, helped to refine and standardize all recommendations and their grading across subgroups (Table 1).

The draft recommendations from each subgroup were then formally vetted by task force committee members at the 2010 consensus conference held in Edmonton, Alberta. Based on the deliberations at the consensus conference, the 2010 recommendations were finalized and then submitted to all 63 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; in the actual vote, all recommendations received at least 80% approval.

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 if 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

I. Lifestyle management

Recommendations

A. Physical exercise

1. For nonhypertensive individuals (to reduce the possibility of becoming hypertensive) or for hypertensive patients (to reduce their 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).
2. Maintenance of a healthy body weight (body mass index 18.5 kg/m^2 to 24.9 kg/m^2, and waist circumference 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 employ 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, and that is reduced in saturated fat and cholesterol (Dietary Approaches to Stop Hypertension [DASH] diet; Table 2) (grade B).

E. Sodium intake

1. For prevention and treatment of hypertension, a dietary sodium intake of 1500 mg (65 mmol) per day is recommended for adults 50 years of age or younger; 1300 mg (57 mmol) per day if 51 to

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. Trim away fats. 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

70 years of age; and 1200 mg (52 mmol) per day if older than 70 years of age (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).

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 employed (grade B).

Background

Lifestyle modification is a critical component for preventing and treating hypertension. The lifestyle modification guidelines this year include a new recommendation for lower dietary sodium intake targets. The new targets are harmonized with Health Canada's recommendation for daily sodium intake and are consistent with the Institute of Medicine report on dietary reference intake values for electrolytes and water (11). A recently published systematic review of prospective cohort studies found that an 86 mmol (5 g) difference in daily sodium intake was associated with a 23% difference in stroke risk and a 17% difference in total cardiovascular disease risk (9). Evidence from long-term follow-up of two randomized trials showed a 25% to 30% reduction in the risk of cardiovascular events in patients with prehypertension assigned to a sodium reduction intervention (12). Population modelling of reductions in sodium intake from current levels to the targets recommended in the CHEP guidelines are estimated to reduce the prevalence of hypertension in Canada by up to 30% (13).

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 pressures of 100 mmHg or higher (grade A), or average systolic blood pressures of 160 mmHg or higher (grade A) in patients without macrovascular target organ damage or other cardiovascular risk factors.
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).
4. Antihypertensive therapy should be considered in all patients meeting the above indications regardless of age (grade B). Caution should be exercised in elderly patients who are frail.

Background

Because there has not been a substantial change in the evidence base, these guidelines are unchanged from our previous recommendations (14,15).

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 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 options. Useful choices include a thiazide diuretic or CCB with either an ACE inhibitor, ARB or beta-blocker (grade B for the combination of thiazide 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 nondihydropyridine CCB and a beta-blocker (grade D). The combination of an ACE inhibitor and an ARB is not recommended (grade A).
3. Combination therapy using two first-line agents may also be considered as initial treatment of hypertension (grade C) if systolic blood pressure is 20 mmHg above target or if diastolic blood pressure is 10 mmHg above target. However, caution should be exercised in patients in whom a substantial fall in blood pressure from initial combination therapy is more likely to occur or in whom it would be poorly tolerated (eg, elderly patients).
4. If blood pressure is still not controlled with a combination of two or more first-line agents, or there are adverse effects, other antihypertensive drugs may be added (grade D).
5. Possible reasons for a 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

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
Drug interactions
Nonsteroidal anti-inflammatory drugs (including cyclooxygenase-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)
Monoamine oxidase inhibitors, certain selective serotonin reuptake inhibitors and serotonin-noradrenaline reuptake inhibitors
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
Obstructive sleep apnea

Note that causes of 'pseudoresistance' (such as white coat hypertension or pseudohypertension in the elderly) should be ruled out first. Adapted from reference 25

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 options (grade D).
3. If blood pressure is still not controlled with a combination of two or more first-line agents, or 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 a 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); 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.

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 ratio ≥6

If hypertensive patients have three or more of these risk factors, statins should be considered. Derived from reference 26

Background
These recommendations are unchanged from 2009 (14,15).

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 of age), 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).

Background
Because there has not been a substantial change in the evidence base, these guidelines are unchanged from our previous recommendations (14,15). For further guidance, readers are referred to the 2009 Canadian Cardiovascular Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult (16).

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

1. The systolic blood pressure treatment goal is a pressure level of less than 140 mmHg (grade C). The diastolic blood pressure treatment goal is a pressure level of less than 90 mmHg (grade A).

Background
Because there was no substantial change in the evidence base, these guidelines are unchanged from our previous recommendations (14,15).

VI. Treatment of hypertension in association with ischemic heart disease

Recommendations

A. Recommendations for hypertensive patients with coronary artery disease

1. An ACE inhibitor or ARB is recommended for most patients with hypertension and coronary artery disease (grade A).
2. For patients with stable angina, beta-blockers are preferred as initial therapy (grade B). CCBs may also be used (grade B).
3. Short-acting nifedipine should not be used (grade D).
4. For patients with coronary artery disease, but without coexisting systolic heart failure, the combination of an ACE inhibitor and ARB is not recommended (grade B).

5. In high-risk 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 diuretic in selected patients (grade A).

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

1. Initial therapy should include both a beta-blocker and an ACE inhibitor (grade A). An ARB can be used if the patient is intolerant of an ACE inhibitor (grade A in patients with left ventricular systolic dysfunction).
2. 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 radiography (grade D).

Background

ACE inhibitors are recommended for moderate- to high-risk patients with coronary artery disease. This year, CHEP includes ARBs as an option in this setting based on published randomized trials evaluating the role of ARBs in patients with coronary artery disease and hypertension. ONTARGET (4) compared telmisartan 80 mg per day with ramipril 10 mg per day in 25,620 patients with vascular disease or diabetes with end-organ damage. Overall, 75% of patients had a history of coronary disease and 69% had a history of hypertension. The primary outcome was a composite of cardiovascular death, myocardial infarction, stroke or hospitalization for heart failure. During a median follow-up of 56 months, the primary outcome occurred in 16.7% of patients in the telmisartan group and 16.5% of patients in the ramipril group (telmisartan versus ramipril risk ratio [RR] 1.01; 95% CI 0.94 to 1.09). The mean blood pressure throughout the study period was 0.9/0.6 mmHg lower in patients treated with telmisartan than in those treated with ramipril. Adjustment for this small difference in blood pressure did not materially affect the results for the primary outcome (RR 1.02; 95% CI 0.95 to 1.10). Total mortality (RR 0.99; 95% CI 0.91 to 1.07) and the composite of cardiovascular death, myocardial infarction or stroke (RR 0.98; 95% CI 0.90 to 1.07) were similar.

Two additional trials compared ARB with placebo in high-risk patients (5,6). TRANSCEND (5) assigned 5926 patients intolerant to ACE inhibitors to receive telmisartan 80 mg per day or placebo, and outcomes were identical to those studied in ONTARGET (4). At baseline, 77% of patients had a history of hypertension and 75% had coronary artery disease. Throughout the study, blood pressure was lower in the telmisartan group than in the placebo group (mean difference between groups was 4.0/2.2 mmHg). After a median follow-up period of 56 months, the primary outcome occurred in 15.7% of patients in the telmisartan group and 17.0% of patients in the placebo group (telmisartan versus placebo RR 0.92; 95% CI 0.81 to 1.05). The composite of cardiovascular death, myocardial infarction or stroke occurred in 13.0% of patients in the telmisartan group and 14.8% of patients assigned to the placebo group (RR 0.87; 95% CI 0.76 to 1.00). Fewer patients in the telmisartan group (30.3%) were hospitalized for cardiovascular cause compared with the placebo group (33.0%; RR 0.92, 95% CI 0.85 to 0.99).

In a comparison similar to TRANSCEND, PRoFESS (6) assigned 20,332 patients with cerebrovascular disease (74% and 19% of whom had hypertension and extracranial atherosclerosis, respectively) to telmisartan 80 mg per day or placebo in a two-by-two factorial comparison (the other factor being assignment to clopidogrel or low-dose acetylsalicylic acid in combination with extended-release dipyridamole) (6). Throughout the study, the mean blood pressure was 3.8/2.0 mmHg lower in the telmisartan group than in the placebo group. During a mean follow-up period of 2.5 years, the primary outcome of first recurrent stroke occurred in 880 patients (8.7%) in the telmisartan group compared with 934 patients (9.2%) in the placebo group (RR 0.95; 95% CI 0.86 to 1.04). The secondary outcome of stroke, myocardial infarction or death from cardiovascular causes occurred in 1367 patients (13.5%) in the telmisartan group and 1463 patients (14.4%) in the placebo group (RR 0.94; 95% CI 0.87 to 1.01).

The neutral findings in TRANSCEND and PRoFESS likely reflect their low event rate and insufficient power to detect differences between telmisartan and placebo (5,6). In a prespecified pooled analysis of both trials, 12.8% of patients in the telmisartan group experienced a stroke, myocardial infarction or cardiovascular death compared with 13.8% in the placebo group (RR 0.91; 95% CI 0.85 to 0.98); efficacy was particularly accentuated after the first six months of follow-up (RR 0.85; 95% CI 0.78 to 0.92). Collectively, this evidence base provides support for the use of an ARB in patients with hypertension in association with coronary artery disease. However, as was the case before these trials, the accumulated weight of placebo-controlled trial evidence supports the provision of ACE inhibitor therapy for this indication. As in the previous iteration of our guidelines, we continue to discourage the use of combination therapy with both ACE inhibitors and ARBs for most patients, unless other compelling indications exist (such as systolic heart failure) (14,15).

ACCOMPLISH (7,17) enrolled 11,506 patients aged 68.4±6.9 years with hypertension who were at high risk for cardiovascular events by virtue of concomitant coronary artery disease (46%), stroke (13%), renal disease (6%), peripheral arterial disease (8%) or diabetes mellitus (60%). Patients were randomly assigned to receive the combination of benazepril and amlodipine, or the combination of benazepril and hydrochlorothiazide. The primary end point was the composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, hospitalization for angina, resuscitation after sudden cardiac arrest and coronary revascularization. Although control to less than 140/90 mmHg was achieved in a remarkable 74% of trial participants, the mean reduction in blood pressure was slightly greater for the benazepril-amlodipine group than the benazepril-hydrochlorothiazide group (difference of –0.9 mmHg systolic and –1.1 mmHg diastolic; P<0.001 for both systolic and diastolic pressure differences).

The trial was terminated early after a mean follow-up period of 36 months. The primary outcome occurred in 9.6% of patients in the benazepril-amlodipine group compared with 11.8% of patients in the benazepril-hydrochlorothiazide group (hazard ratio 0.80; 95% CI 0.72 to 0.90). Although the majority of these events were coronary revascularization procedures, benazepril-amlodipine was also superior in reducing the risk of hard clinical end points including the traditional composite of death from cardiovascular causes, myocardial infarction and stroke (RR 0.79; 95% CI 0.67 to 0.92). The risk of serious drug-related adverse events was low and similar in both groups. Thus, results of ACCOMPLISH demonstrate the benefits and tolerability of combination therapy in patients with poorly controlled blood pressure. Combination therapy should be individualized and, for selected patients at high risk for cardiovascular events similar to those enrolled in the ACCOMPLISH trial (17), an ACE inhibitor/dihydropyridine CCB combination is preferable to an ACE inhibitor/thiazide diuretic combination.

VII. Treatment of hypertension in association with heart failure

1. 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 class III or IV symptoms of heart failure or postmyocardial 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 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 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 an ACE inhibitor and an ARB due to potential adverse effects such as hypotension, hyperkalemia and worsening renal function (grade C). Additional therapies may also include dihydropyridine CCBs (grade C).

Background

These recommendations are unchanged from previous iterations (14,15).

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 in 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).
3. Following the acute phase of a stroke, patients should have their blood pressure chronically controlled to a target of less than 140/90 mmHg (grade C).
4. Treatment with an ACE inhibitor/diuretic combination is preferred (grade B).
5. For patients with stroke, the combination of an ACE inhibitor and ARB is not recommended (grade B).

Background

These recommendations are unchanged from previous iterations (14,15).

IX. Treatment of hypertension in association with left ventricular hypertrophy

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 diuretics. Direct arterial vasodilators such as hydralazine or minoxidil should not be used.

Background

A new class of antihypertensive agents, the direct renin inhibitors, recently emerged as a potential treatment for hypertension (18). These agents primarily act by blocking renin-dependent cleavage of angiotensinogen to the decapeptide angiotensin I. In 2009, a randomized trial (19) of a direct renin inhibitor (aliskiren) in patients with left ventricular hypertrophy was reported (the Aliskiren in Left Ventricular Hypertrophy [ALLAY] trial). In ALLAY, 465 patients with hypertension, increased ventricular wall thickness and a body mass index of greater than 25 kg/m^2 were assigned to receive aliskiren 300 mg/day, losartan 100 mg/day or a combination of both for nine months. The primary hypothesis in ALLAY was that the combination of aliskiren and losartan would be superior to losartan alone in reducing left ventricular mass index as measured by cardiac magnetic resonance imaging. At nine months, slightly greater reductions in systolic and diastolic blood pressure were seen in the combination group than the two monotherapy groups, but the reduction in left ventricular hypertrophy with combination therapy did not exceed that of patients treated with either therapy alone (P=0.52). To date, no cardiovascular end point data for the direct renin inhibitor class are available; however, four large hard-end point randomized trials are currently in progress (20-23). Given the lack of evidence pertaining to the effects of renin inhibitors on morbidity and mortality, we make no recommendation regarding this class of antihypertensive agents at this time. Recommendations for patients with left ventricular hypertrophy are unchanged from previous iterations (14,15).

TABLE 5
Strategies to improve patient adherence to therapy

Assist your patient to adhere by practicing the following:

- tailor pill-taking to fit patients' daily habits (grade D);
- simplify medication regimens to once-daily dosing (grade D);
- replace multiple-pill antihypertensive combinations with single-pill combinations (grade C);
- use unit-of-use packaging (of several medications to be taken together) (grade D); and
- improve adherence to an antihypertensive prescription through a multidisciplinary team approach (grade B)

Assist your patient in getting more involved in his or her treatment by practicing the following:

- encourage greater patient responsibility/autonomy in monitoring his or her blood pressure and adjusting prescriptions (grade C); and
- educate patients and patients' families about his or her disease and treatment regimens (grade C)

Improve your management in the office and beyond by practising the following:

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

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

1. For patients with nondiabetic chronic kidney disease, the target blood pressure is lower than 130/80 mmHg (grade C).
2. For patients with hypertension and proteinuric chronic kidney disease (urinary protein of greater than 500 mg in 24 h or albumin to creatinine ratio [ACR] of greater than 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 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 may be needed to reach target blood pressures (grade D).
5. The combination of an ACE inhibitor with an ARB is not recommended for patients with nonproteinuric chronic kidney disease (grade B).

Background

These recommendations are unchanged from previous iterations (14,15).

XI. Treatment of hypertension in association with renovascular disease

1. Renovascular hypertension should be treated in the same manner as hypertension without compelling indications, except for caution in the use of ACE inhibitors or ARBs due to the risk of acute renal failure in bilateral disease or unilateral disease with a solitary kidney (grade D).
2. 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).

TABLE 6
Considerations in the individualization of antihypertensive therapy

Consideration	Initial therapy	Second-line therapy	Notes and/or cautions
Hypertension without other compelling indications (target blood pressure <140/90 mmHg)			
Diastolic ± systolic hypertension	Thiazide diuretics, beta-blockers, ACE inhibitors, ARBs or long-acting CCBs (consider ASA and statins in selected patients). Consider initiating therapy with a combination of first-line drugs if the blood pressure is ≥20 mmHg systolic or ≥10 mmHg diastolic above target	Combinations of first-line drugs	Beta-blockers are not recommended as initial therapy in those older than 60 years of age. Hypokalemia should be avoided by using potassium-sparing agents in those who are prescribed diuretics as monotherapy. ACE inhibitors are not recommended in black patients. 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	Thiazide diuretics, ARBs or long-acting dihydropyridine CCBs	Combinations of first-line drugs	Same as diastolic ± systolic hypertension
Diabetes mellitus (target blood pressure <130/80 mmHg)			
Diabetes mellitus with albuminuria*	ACE inhibitors or ARBs	Addition of thiazide diuretics, cardioselective beta-blockers, long-acting CCBs	If the serum creatinine level is >150 µmol/L, a loop diuretic should be used as a replacement for low-dose thiazide diuretics if volume control is required
Diabetes mellitus without albuminuria*	ACE 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	Normal albumin to creatinine ratio <2.0 mg/mmol in men and <2.8 mg/mmol in women Combination of an ACE inhibitor with an ARB is specifically not recommended
Cardiovascular disease (target blood pressure <140/90 mmHg)			
Coronary artery disease	ACE inhibitors or ARBs (except in low-risk patients); beta-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
Previous myocardial infarction	Beta-blockers, ACE inhibitors (ARBs if ACE inhibitor intolerant)	Long-acting CCBs	Combination of an ACE inhibitor with an ARB is specifically not recommended
Heart failure	ACE inhibitors (ARBs if ACE inhibitor intolerant) and beta-blockers. Spironolactone in patients with NYHA class III or IV symptoms	ARB in addition to ACE inhibitor. Hydralazine/isosorbide dinitrate combination Thiazide or loop diuretics are recommended as additive therapy	Titrate doses of ACE inhibitors and ARBs to those used in clinical trials. Avoid nondihydropyridine CCBs (diltiazem, verapamil). Monitor potassium and renal function if combining an ACE inhibitor with an ARB
Left ventricular hypertrophy	Does not affect initial treatment recommendations	Combination of additional agents	Hydralazine and minoxidil can increase left ventricular hypertrophy
Past stroke or TIA	ACE inhibitor/diuretic combinations	Combination of additional agents	This does not apply to acute stroke. Blood pressure reduction reduces recurrent strokes in stable patients. Combination of an ACE inhibitor with an ARB is specifically not recommended
Nondiabetic chronic kidney disease (target blood pressure <130/80 mmHg)			
Nondiabetic chronic kidney disease with proteinuria†	ACE inhibitors (ARBs if ACE inhibitor intolerant) if there is proteinuria 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. Combinations of an ACE inhibitor and an ARB are specifically not recommended in patients with chronic kidney disease without proteinuria
Renovascular disease	Does not affect initial treatment recommendations	Combinations of additional agents	Avoid ACE inhibitors or ARB if bilateral renal artery stenosis or unilateral disease with solitary kidney
Other conditions (target blood pressure <140/90 mmHg)			
Peripheral arterial disease	Does not affect initial treatment recommendations	Combinations of additional agents	Avoid beta-blockers with severe disease
Dyslipidemia	Does not affect initial treatment recommendations	Combinations of additional agents	–
Overall vascular protection	Statin therapy for patients with three or more cardiovascular risk factors or atherosclerotic disease Low-dose ASA in patients with controlled blood pressure	–	Caution should be exercised with the ASA recommendation if blood pressure is not controlled

**Albuminuria is defined as a persistent albumin to creatinine ratio of greater than 2.0 mg/mmol in men and greater than 2.8 mg/mmol in women; †Proteinuria is defined as urinary protein greater than 500 mg in 24 h or albumin to creatinine ratio greater than 30 mg/mmol. ACE Angiotensin-converting enzyme; ARB Angiotensin receptor blocker; ASA Acetylsalicylic acid; CCB Calcium channel blocker; NYHA New York Heart Association; TIA Transient ischemic attack*

Background
These recommendations are unchanged from previous iterations (14,15).

XII. Treatment of hypertension in association with diabetes mellitus

1. Persons with diabetes mellitus should be treated to attain systolic blood pressures of less than 130 mmHg (grade C) and diastolic blood pressures of less than 80 mmHg (grade A). (These target blood pressure levels are the same as the blood pressure treatment thresholds.) Combination therapy using two first-line agents may also be considered as initial treatment of hypertension (grade B) if systolic blood pressure is 20 mmHg above target or if diastolic blood pressure is 10 mmHg above target. However, caution should be exercised in patients in whom a substantial fall in blood pressure is more likely or poorly tolerated (eg, elderly patients and patients with autonomic neuropathy).
2. For persons with diabetes and normal urinary albumin excretion (ACR of less than 2.0 mg/mmol in men and less than 2.8 mg/mmol in women) and without chronic kidney disease, with blood pressures of 130/80 mmHg or higher despite lifestyle interventions, any one of the following are recommended: an ACE inhibitor (grade A for persons 55 years of age or older, and grade B for persons younger than 55 years of age), an ARB (grade A for persons with left ventricular hypertrophy and 55 years of age or older, and grade B for persons without left ventricular hypertrophy irrespective of age), a dihydropyridine CCB (grade A for persons 55 years of age or older, and grade B for persons younger than 55 years of age), or a thiazide or thiazide-like diuretic (grade A for persons 55 years of age or older, and grade B for persons younger than 55 years), 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) can be substituted. Additional antihypertensive drugs should be used if target blood pressure levels are not achieved with standard-dose monotherapy (grade B). The combination of an ACE inhibitor with an ARB is not recommended in patients with diabetes and normal urinary albumin levels (grade B).
3. For persons with diabetes and albuminuria (persistent ACR of greater than 2.0 mg/mmol in men or 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 at 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.
4. For persons with diabetes and a normal urinary albumin excretion rate (ACR of less than 2.0 mg/mmol in men or less 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 or thiazide-like diuretic (grade C).
5. Alpha-blockers are not recommended as first-line agents for the treatment of hypertension in persons with diabetes (grade A).

Background
These recommendations are unchanged from previous iterations (14,15).

XIII. Adherence strategies for patients

1. Adherence to an antihypertensive prescription can be improved by a multipronged approach (Table 5).

Background
This year, we strengthen our recommendation for replacing multiple antihypertensive agents with fixed-dose combination therapy (grade C; Table 5). To limit pill burden, patients taking several pills should ideally be treated with single-pill combinations. Clinicians can achieve this by converting short-acting drugs to once-daily agents and adopting combination therapy whenever possible. In the recent Simplified Treatment Intervention to Control Hypertension (STITCH) trial (8), 2104 patients with uncontrolled hypertension in 45 family practices in southwestern Ontario were randomly assigned, at the practice level, to receive either simplified treatment consisting of fixed-dose combination therapy with a low-dose ACE inhibitor or ARB and diuretic combination, or management according to prevailing hypertension guidelines. The proportion of patients achieving target blood pressure was significantly higher in the simplified treatment group (64.7% versus 52.7%; absolute difference 12.1% [95% CI 1.5% to 22.4%]). These data should be viewed in concert with supportive results from a meta-analysis of 42 randomized trials showing that the incremental blood pressure reduction achieved by combining drugs from two different classes (ie, combination therapy) is approximately five times greater than doubling the dose of one drug (ie, step therapy) (24).

XIV. Treatment of secondary hypertension due to endocrine causes

1. Treatment of hyperaldosteronism and pheochromocytoma are outlined in Online Tables 1 and 2. (Online tables are available at www.canjcardiol.com or www.pulsus.com.)

Background
Because there has been no substantive change in the evidence base this past year, the recommendations for this section are unchanged (14,15).

FUTURE DIRECTIONS

The present paper (see Table 6 for the summary) represents the 11th iteration of the annually updated CHEP recommendations for the management of hypertension and we will continue to conduct yearly systematic reviews of the clinical trial evidence to annually update our recommendations for therapy.

APPENDIX
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Pharmacotherapy for Hypertensive Patients with Cardiovascular Disease: S Rabkin (Chair), M Arnold, G Moe, J Howlett

Echocardiography: G Honos (Chair)

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Pharmacotherapy for Hypertensive Patients with Cerebrovascular Disease: P Lindsay (Chair), J-M Boulanger, M Sharma

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ONLINE TABLE 1
Treatment recommendations for patients with hyperaldosteronism

- Treatment of confirmed unilateral aldosterone-producing adenoma (APA) is surgical removal by laparoscopic adrenalectomy
- Patients should be treated for eight to 10 weeks before surgery to correct metabolic abnormalities and to 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 to 400 mg per day (usual doses are 100 mg to 200 mg). For those intolerant to spironolactone, amiloride 10 mg to 20 mg per day is an alternative. The 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

ONLINE TABLE 2
Treatment recommendations for patients with pheochromocytoma

- Alpha-blockers (prazosin, doxazosin, terazosin and phenoxybenzamine) should be used as first-line agents in suspected pheochromocytoma. Alpha-methyldopa 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 for 10 to 14 days of phenoxybenzamine (10 mg to 20 mg two to three times daily), prazosin (1 mg to 3 mg two to three times daily), terazosin (2 mg to 10 mg two times daily) or doxazosin (2 mg to 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 to 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 performed under alpha and beta blockade (as above), followed immediately by tumour resection. In late pregnancy, alpha and beta blockade, followed by elective caesarean section and immediate tumour 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, terazosin) plus beta blockade and/or tyrosine hydroxylase inhibition with metyrosine. A combination of cyclophosphamide, vincristine and dacarbazine may be used for chemotherapy for metastatic pheochromocytoma. Treatment with high-dose iodine-131 metaiodobenzylguanidine induces only a moderate response, but may help control blood pressure