The 2009 Canadian Hypertension Education Program recommendations for the management of hypertension: Part 2 – therapy

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NA Khan, B Hemmelgarn, RJ Herman, et al; for the Canadian Hypertension Education Program. The 2009 Canadian Hypertension Education Program recommendations for the management of hypertension: Part 2 – therapy. *Can J Cardiol* 2009;25(5):287-298.

OBJECTIVE: To update the evidence-based recommendations for the prevention and management of hypertension in adults for 2009.

OPTIONS AND OUTCOMES: For lifestyle and pharmacological interventions, evidence from randomized controlled trials and systematic reviews of trials was 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 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 2007 to August 2008 to update the 2008 recommendations. To identify additional published 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 less than 2300 mg (100 mmol)/day (and 1500 mg to 2300 mg [65 mmol 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 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 conditions. Blood pressure

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Received for publication February 26, 2009. Accepted March 5, 2009

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. 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, 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 patients who are not black), 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 as the initial treatment of hypertension if the systolic blood pressure is 20 mmHg above the target or if the diastolic blood pressure is 10 mmHg above the target. The combination of ACE inhibitors and ARBs should not be used. 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 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. 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 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 2009 du Programme d'éducation canadien sur l'hypertension pour la prise en charge de l'hypertension : 2^e partie – le traitement

OBJECTIF : Mettre à jour les recommandations probantes pour la prévention et la prise en charge de l'hypertension chez les adultes en 2009.

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 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 2007 et août 2008 afin de mettre les recommandations de 2008 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 2 300 mg (100 mmol)/jour (et à entre 1 500 mg et 2 300 mg [entre 65 mmol/jour et 100 mmol/jour pour les hypertendus], à pratiquer des activités aérobiques de 30 à 60 minutes 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 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 adultes 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, 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 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. D'autres médicaments conviennent au traitement de première intention de l'hypertension systolique isolée, y compris les IC dihydropyridines 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 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. 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. Une fois la tension artérielle stabilisée, un traitement à l'acide acétylsalicylique pourra être envisagé.

VALIDATION : Toutes les recommandations sont classées selon la solidité des données probantes, et les 57 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 95 %. Les présentes lignes directrices continueront d'être mises à jour chaque année.

Hypertension affects one in five Canadian adults and the majority of these patients will require pharmacological therapy to control their blood pressure (1,2). Each year, the Canadian Hypertension Education Program (CHEP) Recommendations Task Force reviews recently published hypertension pharmacological and nonpharmacological treatment studies in an effort to alert primary care providers to new clinical advances in the management of hypertension. Equally important is the review of studies that indicate the potential harm of certain therapies for hypertension patients.

This year, recent publication of the landmark study, HYpertension in the Very Elderly Trial (HYVET) (3) resulted in new recommendations on treatment of hypertension in the very old, and the ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) studies (4,5) demonstrate harm associated with combination angiotensin-converting enzyme (ACE) inhibitor and angiotensin receptor antagonist (ARB) therapy. We also discuss other key hypertension trials – the Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation (ADVANCE) trial (6), the Telmisartan Randomized Assessment Study in ACE-Intolerant Subjects with Cardiovascular Disease (TRANSCEND) (7), and the Prevention Regimen For Effectively Avoiding Second Strokes (PROFESS) trial (8) – as well as current evidence on the risk of new-onset atrial fibrillation (AF) with antihypertensive therapy.

The present scientific report outlines the complete 2009 recommendations on 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 CHEP makes the assumption that the benefits are generalized 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.

METHODS

A Cochrane collaboration librarian conducted a MEDLINE search using a highly sensitive search strategy for randomized trials and systematic reviews published from 2007 to August 2008. 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 the Canadian Society of Nephrology collaborated with the CHEP subgroup members for the 2009 recommendations process. The subgroups appraised the quality of relevant studies using a standardized algorithm developed by the 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 (Table 1).

The draft recommendations from each subgroup were then formally vetted at the 2008 consensus conference held in Toronto, Ontario, by task force committee members. Based on the deliberations at the consensus conference, the 2009 recommendations were finalized and then 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.

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

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/m² to 24.9 kg/m², and waist circumference smaller than 102 cm for men and smaller 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 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 of hypertension, in addition to a well-balanced diet, a dietary sodium intake of less than 2300 mg (100 mmol) per day is recommended (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. 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>

- In hypertensive patients, dietary sodium intake should be limited to 1495 mg to 2300 mg (65 mmol to 100 mmol) per day (grade B).

F. Potassium, calcium and magnesium intake

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

G. Stress management

- 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 modifications are the mainstay interventions to prevent or delay the onset of hypertension and are an essential concomitant therapy for those who require pharmacological drug treatment for hypertension. Smoking and smokeless tobacco increase the incidence of hypertension (10,11). Furthermore, smoking and hypertension together substantially increase the risk of mortality and confer a greater than additive risk (12). Therefore, smoking cessation counselling and treatment should be provided to all hypertensive patients who smoke.

The recommendations for lifestyle modifications are unchanged this year because there were no substantive changes in the evidence base (13,14).

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

Recommendations

- 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 (see Tables 3 and 4 from Padwal et al, pages 279-286 in this issue of the *Journal*).
- 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).
- 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).

- 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

Randomized trials of antihypertensive therapy demonstrate clear benefit across many subgroups of hypertensive patients (15). However, very elderly patients were largely excluded from these trials. Observational studies raise concern that blood pressure lowering in patients 80 years of age or older may be poorly tolerated and associated with increased mortality (16,17). This year, the landmark HYVET randomized placebo-controlled trial (3) examined the efficacy and safety of antihypertensive therapy in this very elderly population. Hypertensive patients 80 years of age or older, predominantly from Europe and China, without a history of heart failure, dementia, chronic kidney disease or a requirement for nursing home care, were enrolled. A total of 3845 patients with a mean baseline blood pressure of 173/90.8 mmHg were randomly assigned to receive indapamide or a placebo. The indapamide group had a greater mean reduction in blood pressure (−15.0/−6.1 mmHg) than the placebo group. After a median 1.8 years of follow-up, the trial was terminated early with a 30% RR reduction in the primary end point, fatal or nonfatal stroke (95% CI −1% to 51%; $P=0.06$), a 39% reduction in fatal stroke (95% CI 1% to 62%; $P=0.05$) and a 21% reduction in the total mortality (95% CI 4% to 35%; $P=0.02$) in the indapamide group compared with the placebo group. The rate of serious adverse events was higher in the placebo group than the indapamide group. HYVET clearly demonstrates the beneficial effects of antihypertensive therapy in reducing the risk of stroke and death in very elderly patients; these results form the basis of the new recommendation to prescribe antihypertensive therapy regardless of age. However, it is important to note that the selected patients enrolled in HYVET were healthier than the general Canadian population 80 years of age and older (18); therefore, these results may not be extrapolated to elderly patients who require nursing home care or who are frail.

The remaining decision thresholds are unchanged this year from previous iterations of these guidelines (14,19).

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

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

- Initial therapy should be monotherapy with a thiazide diuretic (grade A); a beta-blocker (in patients younger than 60 years, grade B); an ACE inhibitor (in nonblack patients, grade B); long-acting calcium channel blocker (CCB) (grade B); or an ARB (grade B). If there are adverse effects, another drug from this group should be substituted. Hypokalemia should be avoided in patients treated with thiazide diuretic monotherapy (grade C).
- 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 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).
- 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 the target or if diastolic blood pressure is 10 mmHg above the target. However, caution should be exercised in patients in whom a substantial fall in blood pressure

from initial combination therapy is more likely or 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 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 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 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.

Background

Evidence for potential benefits of antihypertensive therapy must be weighed against potential harms when applying trial results to clinical practice. However, clinical trial evidence on harm is published less often or is poorly reported (20). The Consolidated Standards of Reporting Trials (CONSORT) statement (21) has extended their recommendations to help improve the reporting of harm-related evidence. This year, the CHEP has added a grade A recommendation to avoid dual renin angiotensin system (RAS) blockade with ACE inhibitor and ARB based on evidence of harm from the ONTARGET study (4). The ONTARGET study was a large, randomized double-blind trial comparing the effects of the ACE inhibitor ramipril 10 mg/day and the ARB telmisartan 80 mg/day, separately and in combination, in patients who were at least 55 years of age who had established vascular disease or diabetes with organ damage. Among the 25,620 patients randomized and after a median follow-up period of 56 months, the telmisartan (−0.9/−0.6 mmHg) and combination therapy groups (−2.4/−1.4 mmHg) had significantly lower blood pressures than the ramipril monotherapy group. There was no significant difference in the primary outcome (cardiovascular death, myocardial infarction, stroke or hospitalization for congestive heart failure) between the ramipril and telmisartan monotherapy groups or the combination therapy group compared with the ramipril monotherapy group. However, combination therapy was associated with significantly higher rates of discontinuation due to syncope (0.3% versus 0.2%) and renal impairment (13.5% versus

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 45

10.2%) compared with ramipril. From the prespecified secondary end point analysis (5), combination therapy was associated with a significantly increased risk of dialysis, doubling of serum creatinine or death compared with ramipril monotherapy (hazard ratio [HR] 1.09, 95% CI 1.01 to 1.18; $P=0.037$). The findings of this high-quality trial demonstrate that combining full doses of telmisartan and ramipril does not provide additional cardiovascular benefits compared with monotherapy with either agent alone, but does significantly increase the adverse event rate. It is unclear whether less than full doses of these agents in combination causes worsening renal impairment or hypotension. However, randomized trials of heart failure patients also report an increased rate of adverse events from renal impairment with combination ACE inhibitor and ARB at various dosages (22,23). Additionally, the potential benefits or harms of dual RAS therapy that includes novel direct renin inhibitors with ACE inhibitor or ARB are unknown.

First-line antihypertensive agents such as thiazide diuretics and ACE inhibitors have been shown to be similar across large randomized clinical trials for end points such as cardiac mortality, myocardial infarction and stroke (24). There is some evidence suggesting that RAS blockade may have additional pleiotropic benefits in reducing other end points including new-onset AF. AF affects approximately 1% of the general population and 5% of patients 65 years of age and older (25), with rates reported to be

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	
<i>If hypertensive patients have three or more of these risk factors, statins should be considered. Derived from reference 48</i>	

higher among patients with hypertension (25,26). New-onset AF also connotes a worse prognosis, with increased rates of cardiovascular events and all-cause mortality (27-29). RAS inhibition may have a favourable effect on the incidence of new-onset AF because of reduced atrial stretch, lowered end-diastolic left ventricular pressure and prevention of atrial fibrosis (26,30,31). A meta-analysis of the Losartan Intervention For End point reduction in hypertension (LIFE) trial (32), the Captopril Prevention Project (CAPPP) (33) and the Swedish Trial in Old Patients with hypertension-2 (STOP2) trial (34), as well as the the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) study (29), showed that RAS blockade with either ACE inhibitors or ARB therapy was associated with a lower risk of new-onset AF compared with either beta-blockers or CCBs (27). However, the incidence of AF was similar in diuretic and placebo groups in the the Systolic Hypertension in the Elderly Program (SHEP) study analysis (28). To date, these analyses from large trials were derived from studies that did not examine new-onset AF as the primary end point. Furthermore, it is still unclear whether the reduced incidence of AF associated with RAS therapy yields a net reduction in cardiovascular events. In the LIFE study (32), in which 18,044 patients with left ventricular hypertrophy were randomly assigned to receive either losartan or atenolol, there was a significant reduction in composite cardiovascular end points (HR 0.60, 95% CI 0.38 to 0.94; $P=0.03$) and stroke (HR 0.49, 95% CI 0.29 to 0.86; $P=0.01$) among those with new-onset AF treated with losartan compared with atenolol. However, in the VALUE study (29), the reduced incidence of new-onset AF associated with valsartan compared with amlodipine did not translate into a reduction in the primary end point. There are ongoing studies, namely Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto (GISSI)-AF (35), that will examine AF as the primary end point. Until the results of these studies are published or until further data emerge to support a specific antihypertensive agent to reduce overall cardiovascular events by reducing the risk of new-onset AF, the CHEP cannot make any conclusive recommendations at this time. We will continue to monitor this area. The remaining recommendations are unchanged this year and the supporting evidence was discussed in previous recommendations documents (19,36).

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 of age). Caution should be exercised if blood pressure is not controlled (grade C).

Background

Because there has not been a significant change in the evidence base, these recommendations are unchanged (36).

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 has not been a substantial change in the evidence base, these recommendations are unchanged from our 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). 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).

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 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

This year, there is a new grade B recommendation to avoid dual RAS inhibition with combination ACE inhibitor and ARB therapy in patients with coronary artery disease, but without coexisting systolic heart failure. This recommendation is based on extrapolation of evidence of harm from the ONTARGET study (4,5). The ONTARGET study population was a high vascular risk group, with 74% of patients having a history of stable coronary artery disease and 49% having a history of previous myocardial infarction at baseline. Patients with heart failure were excluded from the study; of note, several randomized trials (22,23) demonstrated a reduction in congestive heart failure hospitalizations or mortality with combination ACE inhibitor and ARB therapy.

The CHEP also reviewed TRANSCEND (7), the smaller sister study to ONTARGET. This trial studied 5926 patients with cardiovascular disease or high-risk diabetes who were intolerant of ACE inhibitors. The patients were randomly assigned to receive telmisartan or placebo. Despite a greater blood pressure reduction in the telmisartan group ($-3.2/-1.3$ mmHg) over a mean of 2.5 years, there was no difference in the primary composite outcome of cardiovascular death, myocardial infarction, stroke or hospitalization for heart failure (HR 0.92, 95% CI 0.81 to 1.05; $P=0.2$). There was a modest difference in the prespecified composite secondary outcome of cardiovascular death, myocardial infarction and stroke in the telmisartan group (13.0%) compared with the placebo group (14.8%) (HR 0.87; $P=0.048$). However, this difference became nonsignificant after statistical

adjustments were made for multiple comparisons ($P=0.068$). These results from TRANSCEND do not alter the CHEP recommendations for ischemic heart disease, and ACE inhibitors should continue to be used as first-line agents. The remaining recommendations are unchanged from 2008.

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 ACE inhibitors and ARBs 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 (19,36).

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 who have suffered from a stroke, the combination of an ACE inhibitor and ARB is not recommended (grade B).

Background

Following an ischemic stroke, the risk of recurrent stroke, transient ischemic attack or cardiac event ranges from 5% to 15% per year (37). An ACE inhibitor/diuretic combination was found to be neuroprotective in this population and it was thought that there may be a greater benefit exerted with an ARB (38). The Morbidity and Mortality After Stroke, Eprosartan Compared With Nitrendipine for Secondary Prevention (MOSES) study (39) found that the ARB, eprosartan, reduced the risk of the composite outcome of total mortality, and cardiovascular and cerebrovascular events compared with nitrendipine in patients with a previous stroke. The recent PROFESS study (8), a 2×2 factorial randomized controlled trial, evaluated combination antiplatelet agents and telmisartan versus placebo in 20,332 patients with a recent ischemic stroke. After a mean follow-up period of 2.5 years, the telmisartan group had a lower blood pressure (−3.8/−2.0 mmHg)

compared with the placebo group. However, there was no significant difference between the telmisartan (8.7%) and placebo groups (9.2%) for risk of the primary end point, recurrent stroke, or for the secondary end point, composite cardiovascular events. The negative results of PROFESS may be due, in part, to an insufficient follow-up period because the telmisartan group appeared to have significantly fewer recurrent strokes after a minimum of six months on therapy. Presently, there are insufficient data to provide any conclusive recommendations on ARB monotherapy for the treatment of hypertension in patients with cerebrovascular disease. The ONTARGET study (4) provided an opportunity to evaluate the role of an ACE inhibitor and ARB combination in the cerebrovascular disease population because approximately 20% of the ONTARGET study population had a previous stroke. As discussed earlier, there was no benefit from an ARB and ACE inhibitor combination over ACE inhibitor alone, and combination therapy was further associated with a greater risk for hypotension and renal impairment. Thus, the CHEP has a grade B recommendation to avoid this combination in patients with previous stroke or transient ischemic attack. The remaining recommendations are unchanged from 2008 (36).

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

These recommendations are unchanged from 2008 (36).

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

1. For patients with nondiabetic chronic kidney disease, the target blood pressure is less than 130/80 mmHg (grade C).
2. For patients with hypertension and proteinuric chronic kidney disease (urinary protein level higher than 500 mg in 24 h or albumin to creatinine ratio [ACR] higher than 30 mg/mmol), the 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 and ARB is not recommended for patients with nonproteinuric chronic kidney disease (grade B).

Background

The ONTARGET study investigators conducted a prespecified analysis of a composite renal end point of dialysis, doubling of serum creatinine or death (5). Approximately 20% of the ONTARGET population had chronic kidney disease with an estimated glomerular filtration rate of 60 mL/min/1.73 m² or lower at baseline. However, it is uncertain what proportion of these patients had nondiabetic chronic kidney disease. Risk of the composite renal end point was similar in the telmisartan (13.4%) and ramipril (14.5%) groups (HR 1.00, 95% CI 0.92 to 1.09). These results were consistent across subgroups of patients with and without diabetic nephropathy, micro- and macroalbuminuria, and patients with an estimated glomerular filtration rate of 60 mL/min/1.73 m² or lower. Extrapolating the finding of noninferiority of ACE inhibitors and ARBs to patients with nondiabetic chronic kidney disease, the CHEP has upgraded the

recommendation for the use of an ARB to grade B if there is intolerance to an ACE inhibitor.

Dual RAS inhibition has been shown to significantly reduce proteinuria (40), a surrogate end point for cardiovascular disease and renal impairment, in patients with chronic kidney disease. The Combination Treatment of Angiotensin-II Receptor Blocker and Angiotensin-converting Enzyme Inhibitor in Non-diabetic Renal Disease (COOPERATE) trial (41) found a reduced risk of dialysis with combination therapy compared with monotherapy; however, serious inconsistencies among the data since publication have raised concerns about the validity of the results. The ONTARGET study similarly found greater blood pressure reduction and reduced proteinuria with combination therapy. However, likely through a mechanism independent of proteinuria, full doses of combination therapy were associated with an increased risk of doubling of serum creatinine, dialysis or death compared with ramipril monotherapy. Thus, the CHEP has also recommended that this combination should not be used in patients with nonproteinuric chronic kidney disease.

The number of individuals with end-stage renal disease treated by transplantation and dialysis is expected to double by 2010 (42). Kidney transplant recipients have a high prevalence of hypertension that may either pre-exist from chronic native kidney disease or occur de novo post-transplantation. Dialysis patients also carry a high prevalence of hypertension and other cardiac risk factors, placing them at higher risk for developing cardiovascular disease. Cardiovascular mortality is 10 to 30 times higher in dialysis patients than in the general population (43). Control of hypertension is therefore paramount in these high-risk patients. Care providers should refer to the Canadian Society of Nephrology practice guidelines for managing hypertension in dialysis patients (44). The CHEP recommendations task force is actively working with the Canadian Society of Nephrology to develop future recommendations for these patient populations. The remaining recommendations remain unchanged from previous years (19,36,45).

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).

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

1. Persons with diabetes mellitus should be treated to attain systolic blood pressures lower than 130 mmHg (grade C) and diastolic blood pressures lower 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 an initial treatment of hypertension (grade B) if systolic blood pressure is 20 mmHg above the target or if diastolic blood pressure is 10 mmHg above the 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), 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), dihydropyridine CCB (grade A for persons 55 years of age or older, and grade B for persons younger than 55 years of age), or 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 and ARB is not recommended in patients with diabetes and normal urinary albumin levels (grade B).

3. For persons with diabetes and albuminuria (persistent ACR higher than 2.0 mg/mmol in men and higher 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 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 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

The antihypertensive therapy recommendations for diabetic patients are largely based on trials that use monotherapy with an up-titration of agents to achieve targets. However, there are an increasing number of trials evaluating combination antihypertensive therapy, which is particularly relevant given that two or more antihypertensive agents are often required to achieve target blood pressures. This year, based on the efficacy and safety findings from the ADVANCE trial in diabetic patients (6), and extrapolating from other nondiabetic studies (38,46,47), we have added the new recommendation that combination therapy using two first-line agents is a reasonable option in the initial management of hypertension in diabetic patients. In the blood pressure-lowering arm of the ADVANCE trial, 11,140 patients with type 2 diabetes who were older than 55 years of age, with a history of major vascular disease or vascular risk factors, were randomly assigned to receive perindopril/indapamide versus placebo in addition to current antihypertensive therapy. After a mean follow-up period of 4.3 years, combination therapy was associated with a 5.6/2.2 mmHg greater reduction in blood pressure compared with placebo. There were no significant differences in the macrovascular or microvascular primary end points between combination therapy and placebo. 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. Rates of serious adverse events and permanent discontinuation for hypotension or dizziness were similarly low in combination and placebo groups. Several trials in nondiabetic patients also found combination therapy to be associated with greater blood pressure lowering, reduced rates of cardiovascular end points and low rates of adverse events (38,46). Given the significantly greater blood pressure reductions associated with combination therapy, the CHEP added the proviso that a combination of two first-line agents should be used in patients with significant elevations in blood pressure,

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) (grade D); and
- utilizing 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 during 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) 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 – 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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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, the elderly and patients with autonomic neuropathy).

Combination or add-on agents used to achieve blood pressure targets should be selected from first-line choices. However, the combination of an ACE inhibitor and ARB should not be used in diabetic patients with normal urinary albumin levels. This new grade B recommendation is based on extrapolation of the ONTARGET studies in which 38% of enrolled patients were diabetic. The remaining recommendations are unchanged from previous recommendations (36,45).

XIII. Adherence strategies for patients

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

Background

Because there has been no substantial change in the evidence base this year, the recommendations for this section are unchanged (47).

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 there are arrhythmias 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 – 20 mg two to three times daily), 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 employed 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 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) 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 it may help control blood pressure.

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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 year, the recommendations for this section are unchanged.

FUTURE DIRECTIONS

The present paper (see Table 8 for the summary) represents the 10th 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 update our recommendations for therapy.

SPONSORS: The CHEP 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.

TABLE 8
Considerations in the individualization of antihypertensive therapy

	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 of 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 and cerebrovascular disease (target blood pressure <140/90 mmHg)			
Angina	Beta-blockers; ACE inhibitors, except in low-risk patients	Long-acting CCBs	Avoid short-acting nifedipine. Combination of an ACE inhibitor with an ARB is specifically not recommended
Prior myocardial infarction	Beta-blockers and 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 ARB
Left ventricular hypertrophy	Does not affect initial treatment recommendations	Combination of additional agents	Hydralazine and minoxidil can increase left ventricular hypertrophy
Past cerebrovascular accident or TIA	ACE inhibitor/diuretic combinations	Combination of additional agents	This does not apply to acute stroke. Blood pressure reduction reduces recurrent cerebrovascular events 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 ARB are specifically not recommended in people 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 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 in 24 h or an albumin to creatinine ratio of >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. Reproduced with permission from the Canadian Hypertension Education Program

APPENDIX

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Pharmacotherapy for Hypertensive Patients Without Compelling

Indications: R Herman, P Hamet, G Fodor, G Carruthers, J deChamplain, G Pylpchuk, P Lindsay

Endocrinological Forms of Hypertension: E Schiffrin (Chair)

Renal and Renovascular Hypertension: S Tobe (Chair), K Burns, M Ruzicka, M Vallée, J Prasad

Follow-up on Patients with Hypertension: P Bolli (Chair), G Tremblay

Routine Laboratory Tests: T Wilson (Chair), B Penner, E Burgess

Hypertension and Diabetes: P Larochelle (Chair), L Leiter, C Jones, R Ogilvie, S Tobe, V Woo, R Gilbert

Self Measurement of Blood Pressure: D McKay (Chair), A Chockalingam

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