The 2007 Canadian Hypertension Education Program recommendations for the management of hypertension: Part 2 – therapy

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NA Khan, B Hemmelgarn, R Padwal et al; for the Canadian Hypertension Education Program. The 2007 Canadian Hypertension Education Program recommendations for the management of hypertension: Part 2 – therapy. Can J Cardiol 2007;23(7):539-550.

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

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

EVIDENCE: A Cochrane collaboration librarian conducted an independent MEDLINE search from 2005 to August 2006 to update the 2006 Canadian Hypertension Education Program recommendations. In addition, reference lists were scanned and experts were contacted to identify additional published studies. All relevant articles were reviewed and appraised independently by both content and methodological experts using prespecified levels of evidence.

RECOMMENDATIONS: Dietary lifestyle modifications for prevention of hypertension, in addition to a well-balanced diet, include a dietary sodium intake of less than 100 mmol/day. In hypertensive patients, the dietary sodium intake should be limited to 65 mmol/day to 100 mmol/day. Other lifestyle modifications for both normotensive and hypertensive patients include: performing 30 min to 60 min of aerobic exercise four to seven days per week; maintaining a healthy body weight (body mass index of 18.5 kg/m^2 to 24.9 kg/m^2) and waist circumference (less than 102 cm in men and less than 88 cm in women); limiting alcohol consumption to no more than 14 units per week in men or nine units per week in women; following a diet reduced in saturated fat and cholesterol, and one that emphasizes fruits, vegetables and low-fat dairy products, dietary and soluble fibre, whole grains and protein from plant sources; and considering stress management in selected individuals with hypertension.

For the pharmacological management of hypertension, treatment thresholds and targets should take into account each individual's global atherosclerotic risk, target organ damage and any comorbid conditions: blood pressure should be lowered to lower than 140/90 mmHg in all patients and lower than 130/80 mmHg in those with diabetes mellitus or chronic kidney disease. Most patients require more than one agent to achieve these blood pressure targets. In adults without compelling indications for other agents, initial therapy should include thiazide diuretics; other agents appropriate for first-line therapy

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Received for publication March 26, 2007. Accepted April 6, 2007

for diastolic and/or systolic hypertension include angiotensin-converting enzyme (ACE) inhibitors (except in black patients), long-acting calcium channel blockers (CCBs), angiotensin receptor blockers (ARBs) or beta-blockers (in those younger than 60 years of age). First-line therapy for isolated systolic hypertension includes long-acting dihydropyridine CCBs or ARBs. Certain comorbid conditions provide compelling indications for first-line use of other agents: 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 plus diuretic combination is preferred; in patients with nondiabetic chronic kidney disease, ACE inhibitors are recommended; and in patients with diabetes mellitus, ACE inhibitors or ARBs (or, in patients without albuminuria, thiazides or dihydropyridine CCBs) are appropriate first-line therapies. All hypertensive patients with dyslipidemia should be treated using the thresholds, targets and agents outlined in the Canadian Cardiovascular Society position statement (recommendations for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease). Selected high-risk patients with hypertension 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 2007 du Programme d'éducation canadien sur l'hypertension pour la prise en charge de l'hypertension artérielle : 2e partie – le traitement

BUT : Le Programme a pour but de fournir des recommandations fondées sur des données probantes et mises à jour pour la prévention et la prise en charge de l'hypertension artérielle chez les adultes.

POSSIBILITÉS ET CRITÈRES D'ÉVALUATION : En ce qui a trait au mode de vie et aux interventions pharmacologiques, nous avons procédé à un examen des données provenant d'essais comparatifs hasardisés et d'examens méthodiques d'essais. Les principaux critères d'évaluation étaient les changements de morbidité et de mortalité d'origine cardiovasculaire. Cependant, l'abaissement de la pression artérielle (PA) a été accepté comme principal critère d'évaluation relativement aux interventions touchant au mode de vie compte tenu de l'insuffisance de données sur la morbidité et la mortalité à long terme dans le domaine. Pour ce qui est des patients atteints de néphropathie, l'évolution du dysfonctionnement rénal a aussi été acceptée comme critère d'évaluation clinique pertinent.

DONNÉES PROBANTES : Un bibliothécaire de Collaboration Cochrane a effectué une recherche indépendante dans la base de données MEDLINE, de 2005 à août 2006, afin de mettre à jour les recommandations 2006 du Programme d'éducation canadien sur l'hypertension. On a également dépouillé des listes de références et communiqué avec des experts pour trouver d'autres études publiées. Tous les articles pertinents ont été examinés, puis évalués séparément par des experts en contenu et en méthodologie à l'aide d'une grille prédéterminée d'évaluation des données.

RECOMMANDATIONS : Outre un régime alimentaire équilibré, les modifications relatives aux habitudes alimentaires visant à prévenir l'hypertension artérielle (HTA) comprennent un apport de sodium d'origine alimentaire inférieur à 100 mmol/jour. Chez les personnes hypertendues, la prise de sodium alimentaire devrait se limiter à une consommation de 65 à 100 mmol/jour. À cela s'ajoutent des modifications du mode de vie qui s'appliquent autant aux personnes normotendues qu'aux personnes hypertendues : la pratique d'activités aérobiques, de 30 à 60 min, de 4 à 7 jours par semaine; le maintien d'un poids santé (indice de masse corporelle : 18,5 kg/m^2 – 24,9 kg/m^2) et du tour de taille (< 102 cm pour les hommes; < 88 cm pour les femmes); la limitation de la consommation d'alcool à 14 unités par semaine pour les hommes et à 9 unités par semaine pour les femmes; un régime alimentaire pauvre en graisses saturées et en cholestérol, et riche en fruits et légumes, en produits laitiers à faible teneur en matières grasses, en fibres alimentaires et en fibres solubles, en grains entiers et en protéines d'origine végétale; la maîtrise du stress chez certaines personnes hypertendues.

En ce qui concerne la prise en charge pharmacologique de l'hypertension, la détermination des seuils et des valeurs cibles devrait reposer sur le risque global d'athérosclérose et sur la présence de lésions des organes cibles et de toute autre maladie concomitante chez chaque patient; la PA devrait être abaissée à moins de 140/90 mm Hg chez tous les patients et à moins de 130/80 mm Hg chez les patients atteints de diabète sucré ou d'une néphropathie chronique. L'atteinte de ces valeurs cibles nécessitera, dans la plupart des cas, une association de médicaments antihypertenseurs. Chez les adultes qui ne présentent pas d'indications impératives d'emploi de médicaments particuliers, le traitement de départ devrait comprendre les diurétiques thiazidiques; d'autres médicaments conviennent également au traitement de première intention de l'HTA diastolique ou systolique : les inhibiteurs de l'enzyme de conversion de l'angiotensine (IECA), sauf chez les Noirs; les inhibiteurs calciques (IC) à action prolongée; les antagonistes des récepteurs de l'angiotensine (ARA); et les bêta-bloquants (chez les patients de moins de 60 ans). Le traitement de première intention de l'hypertension systolique isolée comprend les IC dihydropyridiniques à action prolongée ou les ARA. Toutefois, certaines maladies concomitantes constituent des indications impératives d'emploi d'autres médicaments : chez les patients souffrant d'angine de poitrine ou d'insuffisance cardiaque ou ayant subi depuis peu un infarctus du myocarde, les bêta-bloquants et les IECA sont recommandés en première intention; chez les patients présentant une atteinte cérébrale vasculaire, l'association d'un IECA et d'un diurétique est à privilégier; chez les patients atteints d'une néphropathie chronique non diabétique, les IECA sont recommandés; et chez les diabétiques, les IECA ou les ARA (ou, chez les patients ne présentant pas d'albuminurie, les diurétiques thiazidiques ou les IC dihydropyridiniques) conviennent en première intention. Tous les patients hypertendus à la fois dyslipidémiques devraient être traités selon les seuils, les valeurs cibles et les médicaments proposés dans la déclaration de la Société canadienne de cardiologie (recommandations sur le diagnostic et le traitement de la dyslipidémie et la prévention des maladies cardiovasculaires). Un traitement aux statines devrait néanmoins être prescrit à certains patients hypertendus, à risque élevé, qui ne parviennent pas à atteindre les seuils établis pour ce type de traitement, dans la déclaration. L'emploi d'acide acétylsalicylique pourra être envisagé une fois la PA stabilisée.

VALIDATION : Toutes les recommandations ont été cotées en fonction de la fiabilité des données et soumises au vote des 57 membres du groupe de travail sur les recommandations fondées des données probantes du Programme d'éducation canadien sur l'hypertension. Les recommandations présentées dans l'article ont toutes recueilli un consensus d'au moins 95 %. Les présentes lignes directrices continueront à faire l'objet d'une mise à jour annuelle.

Hypertension accounts for up to 66% of stroke (1) and 35% of myocardial infarction in women and 20% of myocardial infarction in men (2). Preventing and controlling hypertension is one of the major strategies for reducing the global burden of cardiovascular disease and death (3). The Canadian Hypertension Education Program (CHEP) is a national knowledge translation strategy that aims to improve hypertension prevention and control in Canada. The CHEP Recommendations Task Force systematically reviews and translates the growing body of hypertension studies annually to give health care providers practical, updated, evidence-based recommendations on the management of hypertension. In this document, we report the 2007 recommendations for lifestyle and pharmacological management of hypertension, as well as the evidence and rationale supporting all new recommendations. Summary documents of these recommendations, along with a

freely downloadable slide kit, are available on The Canadian Hypertension Society Web site (www.hypertension.ca).

This year, there were several important developments in the recommendations and recommendations processes. First, the CHEP collaborated with the Canadian Diabetes Association (CDA) and the Canadian Society of Nephrology (CSN) to harmonize blood pressure recommendations across these national guideline bodies. The CDA and the CSN joined the CHEP subgroups to appraise the evidence and draft unified hypertension recommendations.

Another area of focus was promoting dietary changes and reducing dietary salt intake in normotensive individuals to prevent or delay the onset of hypertension. Preventing hypertension is a critical part of overall hypertension control, and even small reductions in blood pressure on a population level are estimated to substantially reduce cardiovascular disease (4,5). The new recommendations were based on the recent publications of three randomized trials on dietary interventions (6-8) and a large meta-analysis (9) of sodium restriction among normotensive individuals.

Because the majority of hypertensive patients require more than a single agent to reach target blood pressure levels, the CHEP also expanded the recommendations for combination therapy in the treatment of hypertension in patients without compelling indications for other agents based on results from the Felodipine EVEnt Reduction (FEVER) trial (10) and the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) study (11).

Although we discuss specific antihypertensive agents in reviewing hypertension trials, all recommendations specify drug classes unless there is compelling evidence that any trial-proven benefits are not a class effect. 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

The methods for the 2007 recommendations are outlined in detail in the current issue of the *Journal* (pages 529-538). In brief, a Cochrane collaboration librarian conducted a MEDLINE search using a highly sensitive search strategy for randomized trials and systematic reviews published in 2005 to August 2006. 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 (Table 2 in pages 551-555 in the current issue of the *Journal*), reviewed all identified articles relevant to their topic area. Members of the CDA Guidelines Committee and the CSN collaborated with the CHEP subgroup members for the 2007 recommendations process. The subgroups appraised the quality of any recommendations arising from relevant articles using a standardized scheme (Figures 2 to 5 in pages 551-555 of the current issue of the *Journal* [12]). Subsequently, the central review committee, composed of epidemiologists (Table 2 on page 552 of the current issue of the *Journal*), 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).

A consensus conference was held in Toronto, Ontario, in September 2006 to review and debate the draft recommendations from each subgroup. Based on discussions at the consensus conference, the 2007 recommendations were finalized and submitted to all 57 voting members of the CHEP Evidence-Based Recommendations Task Force for approval. As in previous years, only those recommendations approved by more than 70% of the task force members 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 (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 (BMI) calculated in all adults (Grade D).

2. Maintenance of a healthy body weight (BMI of 18.5 kg/m^2 to 24.9 kg/m^2; waist circumference of less than 102 cm for men and less than 88 cm for women) is recommended for nonhypertensive individuals to prevent hypertension (Grade C) and for hypertensive patients to reduce blood pressure (Grade B). All overweight hypertensive individuals should be advised to lose weight (Grade B).

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

C. Alcohol consumption

1. To reduce blood pressure, alcohol consumption should be in accordance with Canadian low-risk drinking guidelines in both normotensive and hypertensive

TABLE 2
Dietary Approaches to Stop Hypertension (DASH) eating plan

Food group	Servings	Examples and notes
Grains	7–8/day	Whole wheat bread, oatmeal, popcorn
Vegetables	4–5/day	Tomatoes, potatoes, carrots, beans, peas, squash, spinach
Fruits	4–5/day	Apricots, bananas, grapes, oranges, grapefruit, melons
Low-fat or fat-free dairy foods	2–3/day	Fat-free (skim) or low-fat (1%) milk, fat-free or low-fat yogurt, fat-free or low-fat cheese
Meats, poultry, fish	≤2/day	Select only lean meats, and trim away 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>

individuals. Healthy adults should limit alcohol consumption to two drinks or less per day, and consumption should not exceed 14 standard drinks per week in men and nine standard drinks per week in women (Grade B). (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 proteins from plant sources, and one that is reduced in saturated fats and cholesterol (Dietary Approaches to Stop Hypertension [DASH] diet; Table 2) (Grade B).

E. Salt intake

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

F. Potassium, calcium and magnesium intake

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

G. Stress management

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

Background

Lifestyle modifications can lower blood pressure from 2 mmHg to 11 mmHg (13), which is comparable with the blood pressure-lowering effect of a single antihypertensive agent (14,15). Lifestyle therapy also reduces the incidence of type 2 diabetes mellitus (16), and improves lipid levels (17) and overall quality of life (18). Given these benefits, lifestyle modification is a key strategy for the prevention and treatment of hypertension (3).

Feeding studies have demonstrated that DASH-type diets lower blood pressure (19). Such diets are low in sodium and saturated fat and are rich in potassium, calcium, magnesium and fibre, all of which are factors that likely contribute to blood pressure reduction (20). Several recent randomized controlled feeding studies (6-8) found that diets rich in plant proteins or monounsaturated fats also appear to be beneficial in lowering blood pressure. The OmniHeart trial (6) compared blood pressure changes in 164 individuals fed carbohydrate-rich, protein-rich (mainly derived from plant sources such as soybean) or monounsaturated fat-rich diets in a randomized, three-period crossover study. Despite having a similar caloric intake, individuals consuming a diet rich in protein or monounsaturated fat demonstrated greater mean blood pressure reductions from baseline compared with those consuming a diet rich in carbohydrates (protein-rich diet: –8.0/4.4 mmHg, monounsaturated fat diet: –7.7/3.9 mmHg, versus carbohydrate-rich diet: –7.0/3.6 mmHg among normotensive patients). Blood pressure reductions were more pronounced in hypertensive individuals.

In 2007, the recommendation for reduced salt intake to prevent hypertension has been broadened to apply to all individuals, not just those most likely to be salt-sensitive (black Canadians, patients with renal disease or diabetes, obese individuals and those older than 45 years of age). This was done after careful consideration of the pros and cons of population-wide sodium restriction. The task force recognizes the potential drawbacks of salt deficiency such as fatigue, hyponatremia and iodine deficiency. However, these harmful effects are unlikely with a salt restriction threshold of 100 mmol/day (2300 mg of sodium or 5750 mg of sodium chloride per day) (6). Although the benefits of reducing sodium are attenuated in patients who are already consuming diets rich in potassium or similar to DASH-type diets (20), most individuals do not consume diets that are similar to the DASH eating plan (21). The task force concluded that the preponderance of higher-quality evidence favoured population-wide salt-restriction (9,22,23). He and MacGregor (9) recently conducted a systematic review of 11 randomized controlled trials with 2220 normotensive patients randomly assigned to modest salt reduction for at least four weeks. Although there was heterogeneity across trials, modest salt reduction lowered blood pressure by 2/1 mmHg among normotensive patients. On a population-wide level, even this small reduction is estimated to reduce the risk of stroke deaths by 6% and ischemic heart disease deaths by 4% (4,5).

The remaining recommendations for lifestyle modifications are unchanged this year because there were no substantive changes in the evidence base (24,25).

II. Indications for drug therapy in adults with hypertension who do not have 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 (Tables 3 and 4 on page 533 of the current issue of the *Journal*).

2. Antihypertensive therapy should be strongly considered if diastolic blood pressure readings average 90 mmHg or higher in the presence of macrovascular target organ damage or other independent cardiovascular risk factors (Grade A).

3. Antihypertensive therapy should be strongly considered if systolic blood pressure readings average 140 mmHg or higher in the presence of macrovascular target organ damage (Grade C for 140 mmHg to 160 mmHg; Grade A for higher than 160 mmHg).

Background

The decision to initiate antihypertensive drug therapy is predicated on the patient's total cardiovascular risk. These decision thresholds are unchanged this year because there were no substantive changes in the evidence base described in previous iterations of these guidelines (25,26).

III. Choice of therapy for adults with hypertension who do not have compelling indications for specific agents

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 choices. Useful choices include a thiazide diuretic or CCB with either an ACE inhibitor, an ARB or a beta-blocker (Grade B for the combination of thiazide diuretic with a dihydropyridine CCB, Grade C for the combination of dihydropyridine CCB and an ACE inhibitor, and Grade D for all other combinations). Caution should be exercised in combining a nondihydropyridine CCB and a beta-blocker (Grade D).

3. If blood pressure is still not controlled with a combination of two or more first-line agents, or if there are adverse effects, other antihypertensive drugs may be added (Grade D).

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 'pseudoresistance' (such as white coat hypertension or pseudohypertension in elderly patients) should be ruled out first. Adapted from reference 36

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 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); 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

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 artery disease
Previous stroke or transient ischemic attack
Microalbuminuria or proteinuria
Diabetes mellitus
Smoking
Family history of premature cardiovascular disease
Total cholesterol to high-density lipoprotein cholesterol ratio ≥6

**If hypertensive patients have 3 or more of these risk factors, statins should be considered. Derived from reference 43*

effects, another drug from this group should be substituted. Hypokalemia should be avoided in patients treated with thiazide diuretic monotherapy (Grade C).

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

3. If blood pressure is still not controlled with a combination of two or more first-line agents, or if there are adverse effects, other classes of drugs (such as alpha-blockers, ACE inhibitors, centrally acting agents, or nondihydropyridine CCBs) may be added or substituted (Grade D).

4. Possible reasons for poor response to therapy (Table 3) should be considered (Grade D).

5. Alpha-blockers are not recommended as first-line agents for uncomplicated isolated systolic hypertension (Grade A); 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

Antihypertensive drug therapy is associated with a 20% to 25% reduction in cardiovascular events and a 10% reduction in mortality (27,28). To achieve these substantial cardiovascular benefits, patients often require multiple antihypertensive agents. In recognition of the need for multidrug therapy, combination and add-on therapy trials are emerging. This year, the task force added a new drug combination of a thiazide diuretic with a dihydropyridine CCB for patients who have not achieved target blood pressure with antihypertensive monotherapy based on the results of the FEVER trial (10). In this study, 9711 hypertensive patients from China, 50 to 79 years of age with either established cardiovascular disease or two cardiovascular risk factors, were initiated on low-dose hydrochlorothiazide after a washout of all previous agents. Patients were subsequently randomly assigned to additional low-dose felodipine or placebo, with the option of further open-label antihypertensive agents to maintain a blood pressure of lower than 160/95 mmHg. Those randomly assigned to felodipine plus hydrochlorothiazide had lower blood pressure (138.1/82.3 mmHg), compared with those assigned placebo plus hydrochlorothiazide (141.1/83.9 mmHg), and a significantly lower risk of fatal or nonfatal stroke (hazard ratio [HR] 0.73; 95% CI 0.60 to 0.89) after a mean follow-up period of 3.3 years. Although it was unclear whether imaging was used to ascertain the primary outcome of stroke, there was a consistent benefit favouring felodipine plus hydrochlorothiazide for secondary end points, including cardiovascular events (HR 0.73; 95% CI 0.61 to 0.86) and total mortality (HR 0.69; 95% CI 0.54 to 0.89). These results, demonstrating the efficacy of a dihydropyridine CCB and diuretic combination, are consistent with findings from the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial (11). In this trial, 15,245 patients older than 50 years of age with cardiovascular disease or cardiovascular risk factors were randomly assigned to a valsartan- or an amlodipine-based regimen. Amlodipine and valsartan treatment groups were given hydrochlorothiazide as the first step add-on drug to achieve target blood pressure (25% of the amlodipine group were receiving hydrochlorothiazide in combination). Overall, there was no difference in the primary outcome of cardiac morbidity and mortality (HR 1.03; 95% CI 0.94 to 1.14) between amlodipine- and valsartan-based regimens.

This year, the CHEP removed the specific drug combinations for patients with isolated systolic hypertension given the paucity of evidence for combination therapy in this population. We continue to endorse the general recommendation to choose add-on agents from first-line therapies.

The remaining recommendations are unchanged this year, and the supporting evidence is discussed in the previous recommendations documents (26,29).

IV. Global vascular protection therapy for adults with hypertension who do not have 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 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 (29).

V. Goal of therapy for adults with hypertension who do not have compelling indications for specific agents

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

Background
Because there has not been a substantive change in the evidence base, these recommendations are unchanged from our previous recommendations (26).

VI. Treatment of hypertension in association with ischemic heart disease

A. Recommendations for hypertensive patients with coronary artery disease

1. An ACE inhibitor is recommended for most patients with hypertension and documented coronary artery disease (Grade A).

2. For patients with stable angina, beta-blockers are preferred as initial therapy (Grade B). Long-acting CCBs may also be used (Grade B).

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

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

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

2. Long-acting CCBs may be used in postmyocardial infarction patients when beta-blockers are contraindicated or not effective. Nondihydropyridine CCBs should not be used when there is heart failure, as evidenced by pulmonary congestion on examination or radiograph (Grade D).

Background
It is well established that antihypertensive medications reduce cardiovascular risk among patients with coronary artery disease, and the evidence supporting the choice of agents is unchanged from previous years (24,26). However, a recent analysis of the International Verapamil-Trandolapril Study (INVEST [30]) raises concern about excessive diastolic blood pressure lowering among patients with hypertension and coronary artery disease. In this post hoc analysis of 22,576 patients randomly assigned to either verapamil SR or atenolol, patients with a diastolic pressure below 70 mmHg to 80 mmHg had an associated increased risk of myocardial infarction and death. However, given significant methodological limitations of this analysis, the CHEP thought that a recommendation to avoid reducing diastolic blood pressure below this threshold was not warranted at this time.

Please also note that while ACE inhibitors reduce cardiovascular events among most patients with coronary artery disease, these benefits do not appear to extend to coronary artery disease patients with low cardiovascular risk (ie, those with normal ejection fraction, adequate coronary revascularization and well-controlled atherosclerotic risk factors).

VII. Treatment of hypertension in association with heart failure

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

2. In patients with systolic dysfunction, ACE inhibitors (Grade A) and beta-blockers (Grade A) are recommended as 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 after myocardial infarction. Other diuretics are recommended as additional therapy if needed (Grade B for thiazide diuretics for blood pressure control, Grade D for loop diuretics for volume control).

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

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

5. For hypertensive patients with hypertension 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 long-acting dihydropyridine CCBs (Grade C).

Background
Because there has been no substantive change in the evidence base this year, the recommendations are unchanged from previous iterations (26,29).

VIII. Treatment of hypertension in association with cerebrovascular disease

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

2. Caution is indicated when deciding whether to lower blood pressure in the acute stroke situation; pharmacological agents and routes of administration should be chosen to avoid precipitous decreases 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 lower than 140/90 mmHg (Grade C).

4. Treatment with an ACE inhibitor plus diuretic combination is preferred (Grade B).

Background
These recommendations are unchanged from 2006 (29).

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 may be pharmacological treatment using ACE inhibitors, ARBs, long-acting CCBs or thiazide diuretics. Direct arterial vasodilators, such as hydralazine or minoxidil, should not be used.

Background

This year, the Recommendations Task Force removed beta-blockers from the list of initial therapies for left ventricular hypertrophy based on the re-evaluation of the Losartan Intervention For Endpoint reduction (LIFE) trial (31). The LIFE trial compared the effect of losartan with atenolol in 9193 patients older than 55 years of age with electrocardiogram-diagnosed left ventricular hypertrophy and hypertension. This study found a significant reduction in the composite end point of death, myocardial infarction or stroke favouring losartan (RR 0.87; 95% CI 0.77 to 0.98), even after accounting for differences in trial blood pressures. Although the superiority of ARBs compared with antihypertensives other than beta-blockers could not be established (thus, the drug classes are not assigned evidence grades), the LIFE trial demonstrated the inferiority of beta-blockers in patients with left ventricular hypertrophy. The remaining recommendations are unchanged from 2006 (29).

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

1. For patients with nondiabetic chronic kidney disease, target blood pressure is lower than 130/80 mmHg (Grade C).

2. For patients with hypertension and proteinuric chronic kidney disease (urinary protein level greater than 500 mg/24 h or albumin to creatinine ratio [ACR] 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 D).

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).

Background

It is well established that elevated levels of urinary protein are associated with progressive decline in renal function (32). This year, the CHEP-CSN collaboration recommended ACE inhibitors as initial therapy for patients with urinary protein excretion greater than 0.5 g/day (or an ACR greater than 30 mg/mmol) rather than for all individuals with nondiabetic chronic kidney disease. This distinction was made based on evidence demonstrating that the response to ACE inhibition is modified by baseline urinary protein excretion. Jafar et al (33) evaluated the response to ACE inhibitors according to baseline urinary protein excretion levels in an individual-level meta-analysis of 11 randomized controlled trials involving 1860 nondiabetic chronic kidney disease patients. ACE inhibitors conferred progressively greater benefits in reducing the risk of developing end stage renal disease with increasing levels of urinary protein excretion beginning at a threshold of approximately 0.5 g/day. Whether the benefits of ACE inhibition extend below this threshold is unknown given the paucity of ACE inhibitor studies evaluating patients with lower urinary protein excretion rates, and the imprecision of urinary protein measurements at these lower levels.

The evidence supporting ARBs as an alternative to ACE inhibitors is derived from patients with baseline urinary protein excretion greater than 0.5 g/day (34). Patients who are initiated on ACE inhibitor or ARB should have their serum creatinine and potassium levels monitored carefully, preferably within the first two weeks of therapy (35). These agents may be continued as long as serum creatinine levels do not rise by more than 30% from baseline, because acute increases generally plateau within two months (35).

For patients with nondiabetic chronic kidney disease but normal or low urinary protein excretion, physicians should select the initial therapy from first-line agents for patients with systolic and/or diastolic hypertension without compelling indications. The remaining recommendations are unchanged from 2006 (26,29,36).

XI. Treatment of hypertension in association with renovascular disease

1. Renovascular hypertension should be treated in the same manner as hypertension in patients who do not have 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 (26).

XII. Treatment of hypertension in association with diabetes mellitus

1. Persons with diabetes mellitus should be treated to attain systolic blood pressures of lower than 130 mmHg (Grade C) and diastolic blood pressures of lower than 80 mmHg (Grade A). (These target blood pressure levels are the same as the blood pressure treatment thresholds.)

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) who do not have chronic kidney disease but who have blood pressures 130/80 mmHg or higher despite lifestyle interventions, the following are recommended: an ACE inhibitor (Grade A for persons 55 years of age or older, Grade B for persons younger than 55 years of age); an ARB (Grade A for persons with left ventricular hypertrophy and age of 55 years or older, Grade B for persons without left ventricular hypertrophy irrespective of age); a dihydropyridine CCB (Grade A for persons 55 years of age or older, Grade B for persons younger than 55 years of age); or a thiazide diuretic (Grade A for persons 55 years of age or older, Grade B for persons younger than 55 years of age). Special consideration should be given to the ACE inhibitors and ARBs, given their additional renal benefits. If these drugs are contraindicated or cannot be tolerated, a cardioselective beta-blocker (Grade B) or a nondihydropyridine CCB (Grade B) may be substituted. 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.

3. For persons with diabetes and albuminuria (persistent ACR of more than 2.0 mg/mmol in men and more than 2.8 mg/mmol in women), an ACE inhibitor or an ARB is recommended as initial therapy (Grade A). If blood pressure remains 130/80 mmHg or higher despite lifestyle interventions and the use of an ACE inhibitor or an 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 less than 2.0 mg/mmol in men and less than 2.8 mg/mmol in women) who have isolated systolic hypertension and no chronic kidney disease, a long-acting dihydropyridine CCB (Grade C) is an alternative initial choice to an ACE inhibitor (Grade B), an ARB (Grade B) or a thiazide 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 choice of antihypertensive agent among patients with diabetes is guided by urinary albumin excretion rates, because urinary albumin excretion is a powerful prognostic marker for the development of kidney and cardiovascular disease among diabetic patients. Microalbuminuria is associated with a two- to fourfold increase in cardiovascular disease (37,38). Thus, accurate measurement of albuminuria is essential for managing hypertension among patients with diabetes. In 2007, the CHEP, in partnership with the CDA, replaced urinary albumin measurement with sex-specific ACR, because the ACR is a more sensitive and specific measure of albumin excretion rate (39). Thus, a random urine ACR, based on a morning urine sample, is recommended as a screening procedure to determine the ACR.

From the prespecified subgroup analysis of the INVEST study (40), the CHEP has added nondihydropyridine CCBs to the list of alternative antihypertensive agents for patients with diabetes and normal urinary albumin excretion. In this analysis, 6400 patients with diabetes, coronary artery disease and hypertension were randomly assigned to verapamil SR or atenolol. After a mean follow-up of 2.7 years, there was no significant difference in the primary composite end point, total mortality, nonfatal myocardial infarction or nonfatal stroke in the verapamil SR and atenolol study groups (RR 1.05; 95% CI 0.92 to 1.19). Although urinary protein measurements were not available and this was a high-risk coronary artery disease population, the CHEP believed that it was reasonable to extrapolate the findings, given that patients with diabetes often have coexisting coronary artery disease (41). This year, the CHEP also adds the caution that patients who are initiated on an ACE inhibitor or an ARB should have their serum creatinine and potassium levels monitored carefully, preferably within the first two weeks of therapy (35). The remaining recommendations are unchanged from 2006 (29,36).

TABLE 5
Strategies to improve patient adherence

Assist your patient to adhere by:

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

Assist patients in getting more involved in their treatment by:

- encouraging greater patient responsibility and 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 telephone or mail), particularly over the first three months of therapy (Grade D);
- coordinating with work-site health care givers to improve monitoring of adherence with pharmacological and lifestyle modification prescriptions (Grade D); and
- using electronic medication compliance aids (Grade D).

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XIII. Concordance strategies for patients

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

Background

Because there has been no substantive change in the evidence base this past year, the recommendations for this section are unchanged (42).

TABLE 6
Treatment recommendations for patients with hyperaldosteronism

- Treatment of confirmed unilateral aldosterone-producing adenoma (APA) includes surgical removal by laparoscopic adrenalectomy.
- Patients should be treated for eight to 10 weeks before surgery to correct metabolic abnormalities and control blood pressure.
- For primary aldosteronism patients with adrenal hyperplasia, bilateral adenoma or increased risk of perioperative complications, treatment is medical.
- Medical treatment should be initiated with spironolactone 25 mg 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. 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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XIV. Treatment of secondary hypertension due to endocrine causes

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

Background

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

FUTURE DIRECTIONS

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

SPONSORS: The Canadian Hypertension Society, Blood Pressure Canada, the Public Health Agency of Canada, The College of Family Physicians of Canada, the Canadian Pharmacy Association, the Canadian Council of Cardiovascular Nurses, and the Heart and Stroke Foundation of Canada.

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-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 the 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) 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.
- In 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 or metastatic pheochromocytoma. Treatment with high-dose iodine-131 metaiodobenzylguanidine induces only a moderate response, but it may help control of blood pressure.

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TABLE 8
Considerations in the individualization of antihypertensive therapy

	Initial therapy	Second-line therapy	Notes and/or cautions
Hypertension without compelling indications for other medications			
Diastolic ± systolic hypertension	Thiazide diuretic, beta-blocker (for patients younger than 60 years of age), ACE inhibitor (in nonblack patients), ARB or long-acting CCB	Combinations of first-line drugs	Initial monotherapy should not include alpha-blockers, beta-blockers in patients 60 years of age or older, or ACE inhibitors in black patients. Hypokalemia should be avoided in those who are prescribed diuretics. Caution should be exercised in combining a nondihydropyridine CCB and a beta-blocker
Isolated systolic hypertension	Thiazide diuretic, ARB or long-acting dihydropyridine CCB	Combinations of first-line drugs	Similar cautions as in diastolic ± systolic hypertension without compelling indications
Global vascular protection therapy	Statin therapy (for patients with 3 or more cardiovascular risk factors or atherosclerotic disease). Low-dose ASA therapy		Caution should be exercised in using ASA if blood pressure is not controlled

continued on next page

TABLE 8 – CONTINUED
Considerations in the individualization of antihypertensive therapy

	Initial therapy	Second-line therapy	Notes and/or cautions
Cardiovascular disease			
Coronary artery disease	Beta-blocker (for patients with stable angina); ACE inhibitor (for most patients)	Long-acting CCB	Avoid short-acting nifedipine
Prior myocardial infarction	Beta-blocker and ACE inhibitor	An ARB may be used if ACE inhibitor-intolerant and left ventricular dysfunction is present. Long-acting CCB if beta-blocker is contraindicated or not effective	Avoid nondihydropyridine CCBs if heart failure also present
Heart failure	ACE inhibitor and beta-blocker; aldosterone antagonist (in selected patients)	ARB if ACE inhibitor-intolerant, hydralazine/isosorbide dinitrate if ACE inhibitor- and ARB-intolerant; if blood pressure not controlled, an ARB may be added to ACE inhibitor. Thiazide or loop diuretics as additive therapy. Long-acting dihydropyridine CCB as additive therapy	If combining an ACE inhibitor and an ARB, monitor for potential adverse events, including hypotension, hyperkalemia and worsening renal function
Cerebrovascular disease	ACE inhibitor/diuretic combination		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
Left ventricular hypertrophy	ACE inhibitor, ARB, long-acting CCB or thiazide diuretic		Avoid direct arterial vasodilators such as hydralazine and minoxidil
Nondiabetic chronic kidney disease			
Nondiabetic chronic kidney disease	ACE inhibitors (for patients with proteinuria*)	ARB if ACE inhibitor-intolerant. Thiazide diuretic as additive antihypertensive therapy; loop diuretics for volume overload	Avoid ACE inhibitors and ARBs if bilateral renal artery stenosis or unilateral disease with solitary kidney
Renovascular disease	Similar to diastolic ± systolic hypertension without compelling indications for other medications		Avoid ACE inhibitors and ARBs if bilateral renal artery stenosis or unilateral disease with solitary kidney
Diabetes mellitus			
Diabetes mellitus without albuminuria	ACE inhibitor, ARB, thiazide diuretic or dihydropyridine CCB	If these drugs are not tolerated, a cardioselective beta-blocker or nondihydropyridine CCB may be used	Avoid alpha-blockers as initial monotherapy
Diabetes mellitus with albuminuria†	ACE inhibitor or ARB	Additional antihypertensive agents should be used to achieve target blood pressures	Avoid alpha-blockers as initial monotherapy

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

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