The 2006 Canadian Hypertension Education Program recommendations for the management of hypertension: Part II – Therapy

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

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. For lifestyle interventions, blood pressure (BP) lowering was accepted as a primary outcome given the lack of long-term morbidity/mortality data in this field. For treatment of patients with kidney disease, the development of proteinuria or worsening of kidney function was also accepted as a clinically relevant primary outcome.

EVIDENCE: MEDLINE searches were conducted from November 2004 to October 2005 to update the 2005 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 content and methodological experts using prespecified levels of evidence.

RECOMMENDATIONS: Lifestyle modifications to prevent and/or treat hypertension include the following: perform 30 min to 60 min of

aerobic exercise four to seven days per week; maintain a healthy body weight (body mass index of 18.5 kg/m² to 24.9 kg/m²) and waist circumference (less than 102 cm for men and less than 88 cm for women); limit alcohol consumption to no more than 14 standard drinks per week in men or nine standard drinks 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; restrict salt intake; and consider stress management in selected individuals. Treatment thresholds and targets should take into account each individual's global atherosclerotic risk, target organ damage and comorbid conditions. BP should be lowered to less than 140/90 mmHg in all patients, and to less than 130/80 mmHg in those with diabetes mellitus or chronic kidney disease (regardless of the degree of proteinuria). Most adults with hypertension require more than one agent to achieve these target BPs. For adults without compelling indications for other agents, initial therapy should include thiazide diuretics. Other agents appropriate for first-line therapy for diastolic hypertension with or without systolic hypertension include beta-blockers (in those younger than 60 years), angiotensin-converting enzyme (ACE) inhibitors (in nonblack patients), long-acting calcium channel blockers or angiotensin receptor antagonists. Other agents for first-line therapy for isolated systolic hypertension include long-acting dihydropyridine calcium channel blockers or angiotensin receptor antagonists. Certain comorbid conditions provide compelling indications for first-line use of other agents: in patients with angina, recent

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myocardial infarction or heart failure, beta-blockers and ACE inhibitors are recommended as first-line therapy; in patients with diabetes mellitus, ACE inhibitors or angiotensin receptor antagonists (or in patients without albuminuria, thiazides or dihydropyridine calcium channel blockers) are appropriate first-line therapies; and in patients with nondiabetic chronic kidney disease, ACE inhibitors are recommended. All hypertensive patients should have their fasting lipids screened, and those with dyslipidemia should be treated using the thresholds, targets and agents recommended by the Canadian Hypertension Education Program Working Group on the management of dyslipidemia and the prevention of cardiovascular disease. Selected patients with hypertension, but without dyslipidemia, should also receive statin therapy and/or acetylsalicylic acid therapy.

VALIDATION: All recommendations were graded according to strength of the evidence and voted on by the 45 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: Blood pressure; Drugs; Guidelines; High blood pressure; Hypertension; Lifestyle interventions

Les recommandations du Programme d'éducation canadien sur l'hypertension 2006 Partie II – Le traitement

OBJECTIF : Fournir des recommandations probantes à jour pour la prise en charge de l'hypertension chez les adultes.

POSSIBILITÉS ET ISSUES : Dans le cadre d'interventions pharmacologiques et touchant le mode de vie, les données probantes tirées d'essais aléatoires et contrôlés et d'analyses systématiques d'essais ont été évaluées de manière préférentielle. 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 maladie rénale, l'apparition d'une protéinurie ou l'aggravation de la fonction rénale était également accepté comme issue primaire pertinente d'un point de vue clinique.

DONNÉES PROBANTES : Des recherches dans MEDLINE ont été exécutées entre novembre 2004 et octobre 2005 afin de mettre les recommandations de 2005 à jour. Les listes de référence ont été dépouillées, et on a communiqué avec des spécialistes pour repérer d'autres études publiées. Tous les articles pertinents ont été analysés et évalués de manière indépendante par des spécialistes du contenu et de la méthodologie, au moyen de niveaux de constatation préétablis.

Hypertension is one of the most common chronic medical disorders in Canada (1). Each year, numerous studies are published that may influence the management of hypertension. To provide health care workers with updated, evidence-based information on lifestyle and pharmacological management for patients with hypertension, the Canadian Hypertension Education Program (CHEP) sponsors annually updated national hypertension recommendations (2). In the present report, we provide the complete 2006 recommendation on the management of hypertension and discuss the rationale supporting all new recommendations. Summary documents of these recommendations, along with a free downloadable slide kit, are available on the Canadian Hypertension Society Web site (<www.hypertension.ca>).

RECOMMANDATIONS : Les modifications au mode de vie pour prévenir ou traiter l'hypertension s'établissent comme suit : de 30 à 60 minutes d'exercice aérobique de quatre à sept jours par semaine, le maintien d'un poids santé (indice de masse corporelle de 18,5 kg/m² à 24,9 kg/m²) et d'un tour de taille sain (moins de 102 cm pour les hommes et de 88 cm pour les femmes), la consommation maximale de 14 unités de boissons alcooliques par semaine chez les hommes et de neuf chez les femmes, le respect d'un régime pauvre en gras saturé et en cholestérol axé sur les fruits, les légumes et les produits laitiers faibles en gras, une consommation restreinte de sel et la gestion du stress (chez certains individus). Les valeurs seuils et les valeurs cibles de traitement doivent tenir compte du risque athérosclérotique global de chaque individu, de l'atteinte des organes cibles et des pathologies comorbides présentes. La tension artérielle doit être abaissée à 140/90 mmHg ou moins chez tous les patients, et à 130/80 mmHg chez les diabétiques et les personnes atteintes d'une maladie rénale chronique (quel que soit le degré de protéinurie). La plupart des adultes hypertendus doivent prendre plus d'un médicament pour atteindre les valeurs cibles de tension artérielle. Chez les adultes sans indication impérative de prendre 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 bêtabloquants (chez les personnes de moins de 60 ans), les inhibiteurs de l'enzyme de conversion de l'angiotensine (ECA, sauf chez les patients noirs), les inhibiteurs calciques à longue durée d'action et les antagonistes des récepteurs de l'angiotensine (ARA). D'autres médicaments conviennent au traitement de première intention de l'hypertension systolique isolée, soit les inhibiteurs calciques de la classe des dihydropyridines à longue durée d'action et les ARA. Certaines pathologies comorbides fournissent des indications convaincantes d'utilisation d'autres médicaments en première intention. Ainsi, 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. Chez les patients diabétiques, les inhibiteurs de l'ECA ou les ARA (ou des diurétiques thiazidiques ou des inhibiteurs calciques de la classe des dihydropyridines chez les patients atteints de diabète sans albuminurie) conviennent. Enfin, chez les patients atteints d'une maladie rénale chronique non diabétique, les inhibiteurs de l'ECA sont recommandés. Tous les patients hypertendus devraient subir un dépistage de la lipidémie à jeun, et ceux qui souffrent de dyslipidémie devraient être traités à l'aide des valeurs seuils et des valeurs cibles et des médicaments recommandés par le groupe de travail du Programme d'éducation canadien sur l'hypertension pour la prise en charge de la dyslipidémie et la prévention des maladies cardiovasculaires. Certains patients hypertendus, avec ou sans dyslipidémie, devraient également recevoir un traitement aux statines ou à l'acide acétylsalicylique.

VALIDATION : Toutes les recommandations ont été classées selon la solidité des données probantes, et les 45 membres du groupe de travail des recommandations du Programme d'éducation canadien sur l'hypertension ont exercé leur vote à cet égard. Toutes les recommandations publiées ont obtenu un consensus d'au moins 95 %. Ces lignes directrices continueront d'être mises à jour chaque année.

The major hypertension studies evaluated for the 2006 recommendations include a meta-analysis of 13 randomized trials (3) comparing beta-blockers with other antihypertensive agents, the Anglo-Scandinavian Cardiac Outcomes Trial – Blood Pressure Lowering Arm (ASCOT-BPLA) trial (4), the Prevention of Events with Angiotensin-Converting Enzyme inhibition (PEACE) trial (5), the EUROpean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease (EUROPA) trial (6), the VALsartan In Acute Myocardial Infarction (VALIANT) trial (7), the Morbidity and Mortality after Stroke, Eprosartan compared with nitrendipine for Secondary prevention (MOSES) trial (8), the Ramipril Efficacy In Nephropathy 2 (REIN 2) trial (9), the prespecified diabetes subgroup analysis of the Antihypertensive

and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) (10), and several recently published studies evaluating fixed dose drug therapy (11), unit-of-use packaging (12) and health practitioner-based telephone contact (13) to improve medication adherence.

Although we discuss specific antihypertensive agents in reviewing these 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 workers must also use their own clinical judgement and consider patient preferences when applying these recommendations.

METHODS

The methods for the 2006 recommendations are similar to previous years and are outlined in detail in the preamble for this series (pages 559 to 564). Briefly, a Cochrane collaboration librarian conducted a MEDLINE search using a highly sensitive search strategy for randomized trials and systematic reviews published between November 2004 and October 2005. To ensure that all relevant studies were included, bibliographies of identified articles were hand searched, and national and international content experts (see Appendix in preamble paper [page 563]) reviewed all identified articles relevant to their topic area. Details of search strategies and retrieved articles are available on request from each of the subgroup chairs.

The members of the subgroups appraised the quality of any recommendations arising from relevant articles using a standardized scheme (see Figures 1 to 3 in preamble paper [pages 560 to 561]) (14). Subsequently, the central review committee that comprised of methodological experts (see Appendix in preamble paper) 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 Montreal in October 2005 (in conjunction with the Canadian Cardiovascular Congress) to review and debate the draft recommendations from each of the subgroups. Based on discussions at the consensus conference, the 2006 recommendations were finalized and then submitted to all 45 voting members of the CHEP Evidence-Based Recommendations Task Force for approval. Only those recommendations approved by more than 70% of the Task Force were included in the final recommendations presented here (none of the consensus recommendations were rejected this year – the recommendation with the lowest level of support still received 95% acceptance).

THE 2006 CHEP RECOMMENDATIONS

I. Lifestyle modifications

Lifestyle modifications are the cornerstone of therapy for the prevention and management of hypertension because they lower blood pressure (BP) (15,16), reduce the incidence of diabetes mellitus (17), reduce lipid levels (18) and improve overall quality of life (19).

a) Physical exercise

- 1) For nonhypertensive individuals, to reduce the possibility of becoming hypertensive, or for hypertensive patients to reduce their BP, prescribe the accumulation of 30 min to 60 min of moderate intensity dynamic exercise (such as walking, jogging, cycling or swimming) four to

TABLE 1
Grading scheme for recommendations

Grade	Definition
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.
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.
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.
D	Recommendations are based on expert opinion alone.

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 (WC) should be measured and body mass index (BMI) calculated for all adults (Grade D).
- 2) Maintenance of a healthy body weight (BMI 18.5 kg/m² to 24.9 kg/m²; WC 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 BP (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 BP, 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 fewer 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 1.5 ounces of 80 proof (40%) spirits, 12 ounces of 5% beer or 5 ounces of 12% wine).

d) Dietary recommendations

- 1) It is recommended that hypertensive patients consume a diet that emphasizes fruits, vegetables and low-fat dairy products and that is reduced in saturated fat and cholesterol (Dietary Approaches to Stop Hypertension [DASH] diet) (Grade B) (Table 2).

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)/low-fat (1%) milk, fat-free/low-fat yogurt, fat-free/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, 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>

e) Salt intake

- 1) In normotensive individuals at increased risk of developing hypertension and considered salt-sensitive, such as Canadians of African descent, persons older than 45 years of age and persons with chronic kidney disease or diabetes, dietary sodium intake should be restricted to less than 100 mmol/day (Grade D).
2. In hypertensive patients, dietary sodium intake should be limited to 65 mmol/day to 100 mmol/day (Grade B).

f) Potassium, calcium and magnesium intake

- 1) Hypertensive patients or normotensive individuals at increased risk of developing hypertension and considered salt-sensitive, such as Canadians of African descent, persons older than 45 years of age, or persons with impaired renal function or diabetes, should ensure an adequate intake of potassium, calcium and magnesium by consuming a diet rich in these micronutrients (Grade D).
- 2) Supplementation of potassium, calcium and magnesium is not recommended for the prevention or treatment of hypertension (Grade B).
- 3) Individuals who require a diet rich in these cations, but who cannot tolerate or afford this diet, should supplement their diet with potassium to obtain a daily intake of more than 80 mmol/day (Grade D).

g) Stress management

- 1) In hypertensive patients in whom stress may be implicated in contributing to BP 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

The recommendations for lifestyle modifications are unchanged this year because there were no substantive changes from the evidence base described in the 2005 recommendations (20).

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

- 1) Antihypertensive therapy should be prescribed for average diastolic blood pressures (DBPs) of 100 mmHg or higher (Grade A) or average systolic blood pressures (SBPs) of 160 mmHg or higher (Grade A) in patients without macrovascular target organ damage or other cardiovascular risk factors (see Figures 4 and 5 from preamble paper [pages 561 to 562]).
- 2) Antihypertensive therapy should be strongly considered if DBP 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 SBP 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

Antihypertensive drug therapy is associated with a 20% to 25% reduction in cardiovascular events and a 10% reduction in mortality (21,22). The indications for drug therapy are unchanged this year because there were no substantive changes in the evidence base described in previous iterations of these guidelines (23,24).

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

a) Global vascular protection therapy for patients with hypertension

- 1) Statin therapy is recommended in hypertensive patients with three or more cardiovascular risk factors as defined in Table 3 (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 patients with hypertension (Grade A in patients older than 50 years). Caution should be exercised if BP is not controlled (Grade C).

b) Individuals with diastolic with or without 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 nonblacks [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

TABLE 3
Cardiovascular risk factors for consideration of statin therapy in nondyslipidemic patients with hypertension*

Risk factor*
Male sex
Age 55 years or older
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 of six or greater

*If hypertensive patients have three or more of these risk factors, statins should be considered. *Derived from the Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm (35)*

be substituted. Hypokalemia should be avoided in patients treated with thiazide diuretic monotherapy (Grade C).

- 2) Additional antihypertensive drugs should be used if target BP levels are not achieved with standard dose monotherapy (Grade B). Add-on drugs should be chosen from first-line choices. Useful choices include a thiazide diuretic or CCB with either an ACE inhibitor, ARB or beta-blocker (Grade D; Grade C for the combination of dihydropyridine CCB and ACE inhibitor). Caution should be exercised when combining a nondihydropyridine CCB and a beta-blocker (Grade D).
- 3) If BP 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).
- 4) Possible reasons for poor response to therapy (Table 4) 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 aged 60 years 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 (Table 5).

c) 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).

TABLE 4
Possible reasons for poor response to therapy in adults with uncomplicated hypertension*

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 haung, 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 the elderly) should be ruled out first. Adapted from reference 23*

- 2) Additional antihypertensive drugs should be used if target BP levels are not achieved with standard dose monotherapy (Grade B). Add-on drugs should be chosen from first-line choices (Grade D). Useful combinations include a thiazide diuretic or dihydropyridine CCB with either an ACE inhibitor or ARB, or beta-blocker (Grade D).
- 3) If BP 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 calcium channel blockers) may be added/substituted (Grade D).
- 4) Possible reasons for poor response to therapy (Table 4) should be considered (Grade D).
- 5) Alpha-blockers (Grade A) are not recommended as first-line agents for uncomplicated isolated systolic hypertension, and beta-blockers (Grade A) are not

TABLE 5
Considerations in the individualization of antihypertensive therapy*

	Initial therapy	Second-line therapy	Notes and/or cautions
Diastolic with or without systolic hypertension without compelling indications for other medications	Thiazide diuretics, beta-blockers (for patients younger than 60 years of age), ACE inhibitors (in nonblacks), ARBs or long-acting CCBs (consider ASA and/or statins in selected patients)	Combinations of first-line drugs	Alpha-blockers are not recommended as initial monotherapy. Beta-blockers are not recommended as initial monotherapy in those aged 60 years or older. ACE inhibitors are not recommended as initial monotherapy in blacks. Hypokalemia should be avoided in those who are prescribed diuretics
Isolated systolic hypertension without other compelling indications	Thiazide diuretics, ARBs, or long-acting dihydropyridine CCBs	Combinations of first-line drugs	Alpha-blockers are not recommended as initial monotherapy. Beta-blockers are not recommended as initial monotherapy in those aged 60 years or older. Hypokalemia should be avoided in people who are prescribed diuretics
Diabetes mellitus with nephropathy	ACE inhibitors or ARBs	Addition of one or more of thiazide diuretics, cardioselective beta-blockers, long-acting CCBs or use of an ARB/ACE inhibitor combination	
Diabetes mellitus without nephropathy	ACE inhibitors, ARBs, thiazide diuretic, or dihydropyridine CCBs	Combination of first-line drugs or addition of cardioselective beta-blocker	
Angina	Beta-blockers (strongly consider adding ACE inhibitors in most patients)	Long-acting CCB	Avoid short-acting nifedipine
Prior myocardial infarction	Beta-blockers and ACE inhibitors	Combinations of additional agents	
Heart failure	ACE inhibitors (ARB if ACE inhibitor-intolerant), beta-blockers, and spironolactone in selected patients	ARB or hydralazine/isosorbide dinitrate; thiazide or loop diuretics as additive therapy	Avoid nondihydropyridine CCBs. If combining an ACE inhibitor and an ARB, monitor for potential adverse events including hypotension, hyperkalemia and worsening renal function
Past cerebrovascular accident or transient ischemic attack	ACE inhibitor/diuretic combinations		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
Nondiabetic chronic kidney disease	ACE inhibitors (diuretics as additive therapy)	Combinations of additional agents (ARBs if ACE inhibitor-intolerant)	Avoid ACE inhibitors and ARBs if bilateral renal artery stenosis is present
Left ventricular hypertrophy	ACE inhibitors, ARBs, CCBs, thiazide diuretics, or beta-blockers for patients younger than 60 years of age		Avoid hydralazine and minoxidil
Peripheral arterial disease	Does not affect treatment recommendations		Avoid beta-blockers with severe disease
Dyslipidemia	Does not affect treatment recommendations		

*Reproduced with permission from the Canadian Hypertension Education Program. ACE Angiotensin-converting enzyme; ARB Angiotensin receptor blocker; CCB Calcium channel blocker

recommended as first-line therapy for isolated systolic hypertension in patients aged 60 years or older; however, both agents may be used in patients with certain comorbid conditions or in combination therapy.

Background

The 2006 recommendations continue to strongly endorse the concept that the reduction of hypertension-related

complications depend more on the extent of BP lowering than on the choice of any specific drug class as first-line therapy for those patients without comorbid conditions which compel a specific drug class choice (such as diabetes mellitus, cardiac disease or renal disease) (22). A recently published meta-analysis of 13 randomized controlled trials (n=105,951) (3) comparing beta-blockers with other antihypertensive agents reported an increased risk of stroke with the use of beta-blockers

(RR increase of 16%, 95% CI 4% to 30%). However, this pooled end point was heterogeneous and largely driven by studies where the mean age of trial patients were 60 years or older. When this analysis was restricted to trials where the mean age was less than 60 years, this risk difference disappeared (25). Furthermore, there were no differences in rates of myocardial infarction (MI) or deaths between beta-blockers and other antihypertensives. Thus, we continue to recommend that beta-blockers should not be used as first-line monotherapy in patients aged 60 years or older, but may be used in patients younger than 60 years of age, or in those with other compelling indications for beta blockade (such as symptomatic coronary disease, recent MI or congestive heart failure), or in those requiring polytherapy to control their BP.

To achieve target BP levels, many patients require more than one antihypertensive agent. The evidence supporting particular add-on therapies and combinations have been based on trials demonstrating their additive hypotensive effect, and are therefore a grade D recommendation. This year, we have upgraded the recommendation for the combination of a dihydropyridine CCB with an ACE inhibitor to grade C based on results of the ASCOT-BPLA trial. In the ASCOT-BPLA trial (4), 19,257 patients aged 40 to 79 years with hypertension and at least three other cardiac risk factors were randomly assigned to amlodipine (with the addition of perindopril as required to achieve target BPs) versus atenolol (adding thiazide diuretic as required). Overall, 50% of patients in the amlodipine arm and 55% of patients in the atenolol arm received combination therapy. Patients assigned to amlodipine/perindopril had greater BP lowering compared with those assigned to atenolol/thiazide; the trial was terminated early because the amlodipine/perindopril group had a significantly lower mortality (RR 0.89, 95% CI 0.81 to 0.99) and a reduction in other secondary end points such as stroke and cardiovascular death compared with the atenolol/thiazide group.

The remaining recommendations are unchanged this year; the supporting evidence is discussed in previous recommendation documents (23,26).

IV. Goal of therapy in adults with hypertension without compelling indications

- 1) The SBP treatment goal is a pressure level of less than 140 mmHg (Grade C). The DBP 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 the 2005 recommendations (23,27).

V. 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 hypertensive patients who have had a recent ST-elevation MI or non-ST segment elevation MI

- 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 (LV) systolic dysfunction).
- 2) Long-acting CCBs may be used in post-MI 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

This year, several trials were published that evaluated treatment of hypertension in association with coronary artery disease. The PEACE trial (5) randomly assigned 8290 patients older than 50 years of age with stable coronary artery disease and with normal or slightly reduced LV function to trandolapril or placebo. The study patients' cardiovascular risk factors were well-controlled at baseline: the mean BP was 133/83 mmHg, cholesterol levels were at target, the majority of patients were taking lipid-lowering agents, beta-blockers and antiplatelet agents, and 72% of patients were revascularized. After 4.8 years of follow-up, there was no difference in the primary end point of death from cardiovascular causes, nonfatal MI or coronary revascularization (hazard ratio [HR] 0.96, 95% CI 0.88 to 1.06) between trandolapril and placebo. These findings seemingly contradict the results of EUROPA (6) and the Heart Outcomes Prevention Evaluation (HOPE) study (28), both of which demonstrated benefit with ACE inhibitor over placebo in patients with coronary artery disease and no heart failure. However, the rate of cardiovascular death in the PEACE placebo group was far lower than in the HOPE study, suggesting that the lack of benefit seen with ACE inhibition in the PEACE trial may be attributed to the lower baseline risk in PEACE participants. Thus, we have not changed the general recommendation supporting ACE inhibitors for patients with coronary disease. However, we have softened the wording of our recommendation this year (in previous years, we had advocated that all patients with coronary artery disease should receive ACE inhibitors) to recognize the fact that patients at low risk of cardiovascular events (ie, those with normal ejection fraction, adequate coronary revascularization and well-controlled atherosclerotic risk factors) may not receive additional benefit from ACE inhibition beyond BP control.

This year, we have added a Grade A recommendation supporting the use of ARBs in patients with recent MI and LV systolic dysfunction if patients are intolerant to ACE inhibitors, based on the VALIANT study results. In the VALIANT study (7), 14,703 patients who had an acute MI complicated by heart failure or LV systolic dysfunction (ejection fraction of 35% or lower) were randomly assigned to valsartan alone, captopril alone or both valsartan and captopril. After a two-year median follow-up, there was no difference among the three groups for the primary end point of death from any cause (captopril versus valsartan; HR 1.00, 95% CI 0.90 to 1.11).

The remaining recommendations are unchanged from the 2005 recommendations and the supporting evidence has been previously described (24,26,27).

VI. Treatment of hypertension in association with heart failure

- 1) Patients with hypertension and evidence of heart failure should have an objective assessment of LV ejection fraction, either by echocardiogram or by nuclear imaging (Grade D).
- 2) In patients with systolic dysfunction, ACE inhibitors (Grade A) and beta-blockers (Grade A) are recommended for initial therapy. Aldosterone antagonists (Grade B) are also recommended for patients with New York Heart Association Class III or IV symptoms of heart failure or post-MI. Other diuretics are recommended as additional therapy (Grade B for thiazide diuretics for BP 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 patients with hypertension and heart failure whose BP is not controlled, an ARB may be added to an ACE inhibitor and other antihypertensive drug treatment (Grade A). Careful monitoring should be used if combining ACE inhibitor and ARB due to potential adverse effects such as hypotension, hyperkalemia and worsening renal function (Grade C). Additional therapies may also include long-acting dihydropyridine CCBs (Grade C).

Background

Although there is evidence of benefit in combining an ARB and ACE inhibitor in selected patients with heart failure (29,30), we have added a caution to the use of this combination and we recommend careful monitoring due to concerns over the increased risks of hypotension, hyperkalemia (particularly in patients who are concomitantly taking aldosterone antagonists) and worsening renal function. Because there has been no substantial change in the evidence base this year, the remaining recommendations are unchanged from prior iterations and the supporting evidence is documented there (26,27).

VII. 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 nondisabling stroke or transient ischemic attack (TIA) (Grade A).
- 2) Caution is indicated in deciding whether to lower BP in the acute stroke situation; pharmacological agents and routes of administration should be chosen to avoid precipitous falls in BP (Grade D).

- 3) Following the acute phase of a stroke, patients should have their BP 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).

Background

It is well established that antihypertensive therapy is associated with substantial reductions in cardiovascular events in patients who have suffered a stroke or TIA. Several recent clinic trials suggest that effective BP treatment may reduce the onset of dementia (31,32) and this matter is under active investigation. In the Systolic Hypertension in Europe (Syst-Eur) trial (31), 2418 patients over 60 years of age with hypertension were randomly assigned to nitrendipine or placebo. After a two-year median follow-up, active treatment reduced the incidence of dementia by 50% (95% CI 0% to 76%; $P=0.05$). In the Perindopril Protection Against Recurrent Stroke (PROGRESS) study (32), 6105 patients with prior stroke or TIA were assigned to either active treatment (perindopril for all participants and indapamide as needed) or matching placebo(s). During a mean follow-up of 3.9 years, there was a nonsignificant reduction in the incidence of the dementia (RR 12%, 95% CI -8% to 28%; $P=0.2$), defined in the *Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition* (DSM-IV) (33), and a significant reduction in cognitive decline, defined as a decline of three or more points in the Mini-Mental State Examination score (RR 19%, 95% CI 4% to 32%).

The recommendations for choice of therapy after stroke remain unchanged even after consideration of the MOSES study. In the MOSES trial (8), 1405 patients with a known cerebrovascular event within the last two years were randomly assigned to eprosartan versus nitrendipine. After a mean follow-up of 2.5 years, there was a significant reduction in the primary end point (a composite of total mortality, all cardiovascular and cerebrovascular events, including TIA or stroke, and including recurrent events) among those assigned eprosartan compared with nitrendipine. However, there were several methodological limitations with this study. For example, the differences found in the primary end point appeared to be driven by multiple events in patients being counted as separate events. When the primary end point was analyzed by time to first event, there was no difference in cerebrovascular events between the two treatment arms. This lack of difference in cerebrovascular events was also found in the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) study (34), where 20% of the study population had previous stroke or TIA. Thus, CHEP felt that, at this time, there was insufficient evidence to warrant altering the choice of therapy for patients with cerebrovascular disease. The remaining recommendations are unchanged from the 2005 recommendations (26).

VIII. Treatment of hypertension in association with LV hypertrophy

- 1) Hypertensive patients with LV 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 LV hypertrophy (Grade D). Initial therapy

can be drug treatment using ACE inhibitors, ARBs, long-acting CCBs, thiazide diuretics or, in those younger than 60 years of age, beta-blockers. Direct arterial vasodilators such as hydralazine or minoxidil should not be used.

Background

Because there was no substantial change in the evidence base this year, these recommendations are unchanged from the 2005 recommendations (26).

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

- 1) For patients with nondiabetic chronic kidney disease, target BP is less than 130/80 mmHg (Grade C).
- 2) For patients with hypertension and chronic kidney disease, 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 BPs (Grade D).

Background

This year, we removed the recommendation to lower BP to a target of less than 125/75 mmHg in patients with proteinuric (greater than 1 g/day) chronic kidney disease in light of new findings from the REIN 2 study (9). In this study, 338 patients with proteinuric (greater than 1 g/day) nondiabetic chronic kidney disease receiving ramipril were randomly assigned to intensive BP control (less than 130/80 mmHg) with the addition of felodipine compared with usual BP control (less than 90 mmHg DBP). After a median follow-up of 19 months, there was no significant difference in the primary end point (development of end-stage renal disease) between the two groups (HR 1.00, 95% CI 0.61 to 1.64). The remaining recommendations are unchanged from the 2005 recommendations (27).

X. Treatment of hypertension in association with renovascular disease

- 1) Renovascular hypertension should be treated in the same manner as uncomplicated hypertension, 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 from the 2005 recommendations (27).

XI. Treatment of hypertension in association with diabetes mellitus

- 1) Persons with diabetes mellitus should be treated to attain SBPs of 130 mmHg or less (Grade C) and DBPs of 80 mmHg or less (Grade A).
- 2) For persons with diabetes and albuminuria (urinary albumin excretion rates over 30 mg/day), an ACE inhibitor or an ARB is recommended as initial therapy (Grade A). If BP remains greater than or equal to 130/80 mmHg despite lifestyle interventions and the use of an ACE inhibitor or ARB, then addition of one or more of a thiazide diuretic, long-acting CCB, or use of an ACE inhibitor and ARB in combination can be considered (Grade D). If an ACE inhibitor or ARB cannot be tolerated, a cardioselective beta-blocker (Grade B), long-acting CCB (Grade C) or thiazide diuretic can be substituted (Grade B).
- 3) For persons with diabetes and normal urinary albumin excretion (less than 30 mg/day) and BP greater than or equal to 130/80 mmHg despite lifestyle interventions, an ACE inhibitor (Grade A for persons 55 years of age or older; Grade B for persons younger than 55 years of age), ARB (Grade A for persons with LV hypertrophy and 55 years of age and older; Grade B for persons without LV hypertrophy irrespective of age), dihydropyridine CCB (Grade A for persons 55 years of age or older; Grade B for persons younger than 55 years of age), or thiazide diuretic (Grade A for persons 55 years of age or older; Grade B for persons younger than 55 years) is recommended, with special consideration to the ACE inhibitor and ARB given their additional renal benefits. If these drugs are contraindicated or cannot be tolerated, a cardioselective beta-blocker (Grade B) can be substituted. Additional antihypertensive drugs should be used if target BP levels are not achieved with standard dose monotherapy (Grade B). Add-on drugs should be chosen from first-line choices.
- 4) For persons with diabetes and a serum creatinine over 150 µmol/L (or a creatinine clearance below 30 mL/min/1.73m²), the choice of antihypertensive drugs is the same as above, except that a loop diuretic should be substituted for a thiazide diuretic if control of volume is desired (Grade D).
- 5) For persons with diabetes and a normal urinary albumin excretion rate (less than 30 mg/day) with isolated systolic hypertension, long-acting dihydropyridine CCBs (Grade C) are alternative initial choices to an ACE inhibitor (Grade B), an ARB (Grade B) or a thiazide diuretic (Grade C).
- 6) Alpha-blockers are not recommended as first-line agents for the treatment of hypertension in persons with diabetes (Grade A).

TABLE 6
Strategies to improve patient adherence***Assist your patient to adhere**

- Tailoring pill-taking to fit patients' daily habits
- Simplifying medication regimens to once-daily dosing
- Replacing two antihypertensive agents with a fixed dose combination (where available and appropriate), provided it is the same combination the patient is already taking
- Utilizing unit-of-use packaging (of several medications to be taken together)

Assist your patient in getting more involved in their treatment

- Encouraging greater patient responsibility/autonomy in monitoring their blood pressure and adjusting their prescriptions
- Educating patients and patients' families about their disease/treatment regimens

Improve your management in the office and beyond

- Assessing adherence to pharmacological and nonpharmacological therapy at every visit
- Encouraging adherence with therapy by health care practitioner-based telephone contact, particularly over the first three months of therapy
- Coordinating with work site health care givers to improve monitoring of adherence with pharmacological and lifestyle modification prescriptions
- Utilizing electronic medication compliance aids

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Background

Based on the recent publication of the diabetes subgroup from the ALLHAT trial (10), dihydropyridine CCBs were added to the list of potential first-line agents for persons with diabetes and normal urinary albumin excretion (less than 30 mg/day). In the ALLHAT study subgroup, there were 13,101 patients with type II diabetes mellitus who were randomly assigned to chlorthalidone, amlodipine or lisinopril. Although SBP was significantly lower among those randomly assigned to chlorthalidone compared with lisinopril or amlodipine, there was no difference in the primary end point of coronary heart disease (HR 0.97, 95% CI 0.86 to 1.10) between amlodipine and chlorthalidone. While this lack of difference was generally consistent for other cardiovascular secondary end points, the study was underpowered to detect differences in the development of end-stage renal disease. Thus, we have added the proviso that ACE inhibitors and ARBs also appear to have renal benefits beyond that expected from their BP-lowering effects, and physicians may wish to consider these additional benefits when selecting first-line agents. The remaining recommendations are unchanged from the 2005 recommendations (25,26).

XII. Concordance strategies for patients

- 1) Adherence to an antihypertensive prescription can be improved by a multipronged approach as outlined in Table 6.

Background

The CHEP 2005 recommendations suggest simplification of the drug regimen as a strategy to improve adherence. This year CHEP added the following recommendation: patients using two or more antihypertensive agents should replace these separate pills with a single tablet containing a fixed-dose

combination (where available and appropriate) to improve patient adherence. In a retrospective analysis of 5732 patients (11) in a managed care organization in the United States, patients who were taking a single component fixed-dose combination of amlodipine/benazapril had significantly better medication adherence compared with those taking a similar regimen but in separate tablets (81% versus 74% adherence; $P < 0.001$). Patients taking fixed-dose combinations also required fewer medical resources (fewer inpatient visits and lower costs of care) than patients receiving the same agents as separate components. CHEP also recommends utilizing unit-of-use medication packaging such as blister packaging or a pill organizer (eg, dosette box) based on the findings of a recently published systematic review (12). Although the patient settings and measures of outcome were heterogeneous in the 12 studies evaluated, these studies suggest that unit-of-use packaging is likely to improve adherence.

This year, we have also added a recommendation in support of health care practitioner-based telephone contact, particularly over the first three months of therapy. This grade D recommendation was based on extrapolation from a small ($n=30$), randomized, controlled trial (13) evaluating the impact of personalized follow-up on compliance with lipid-lowering therapy. Patients randomly assigned to weekly telephone contact for 12 weeks had significantly greater compliance at the end of two years compared with those who did not receive telephone contact. The remaining recommendations for this section are unchanged this year.

FUTURE DIRECTIONS

The present paper represents the seventh iteration of the annually updated CHEP recommendations for the management of hypertension. We will continue to conduct yearly systematic reviews of the clinical trial evidence to annually update our recommendations for therapy.

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