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1999 Canadian recommendations for the management of hypertension

including Case-based applications of the recommendations

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1999 Canadian recommendations for the management of hypertension

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Abstract

Objective: To provide updated, evidence-based recommendations for health care professionals on the management of hypertension in adults.

Options: For patients with hypertension, there are both lifestyle options and pharmacological therapy options that may control blood pressure. For those patients who are using pharmacological therapy, a range of antihypertensive drugs is available. The choice of a specific antihypertensive drug is dependent upon the severity of the hypertension and the presence of other cardiovascular risk factors and concurrent diseases.

Outcomes: The health outcomes considered were changes in blood pressure and in morbidity and mortality rates. Because of insufficient evidence, no economic outcomes were considered.

Evidence: MEDLINE searches were conducted from the period of the last revision of the Canadian Recommendations for the Management of Hypertension (January 1993 to May 1998). Reference lists were scanned, experts were polled and the personal files of the authors were used to identify other studies. All relevant articles were reviewed, classified according to study design and graded according to levels of evidence.

Values: A high value was placed on the avoidance of cardiovascular morbidity and premature death caused by untreated hypertension.

Benefits, harms and costs: The diagnosis and treatment of hypertension with pharmacological therapy will reduce the blood pressure of patients with sustained hypertension. In certain settings, and for specific drugs, blood pressure lowering has been associated with reduced cardiovascular morbidity and mortality.

Recommendations: This document contains detailed recommendations pertaining to all aspects of the diagnosis and pharmacological therapy of hypertensive patients. With respect to diagnosis, the recommendations endorse the greater use of non-office-based measures of blood pressure control (i.e., using home blood pressure and automatic ambulatory blood pressure monitoring equipment) and greater emphasis on the identification of other cardiovascular risk factors, both in the assessment of prognosis in hypertension and in the choice of therapy. On the treatment side, lower targets for blood pressure control are advocated for some subgroups of hypertensive patients, in particular, those with diabetes and renal disease. Implicit in the recommendations for therapy is the principle that for the vast majority of hypertensive patients treated pharmacologically, practitioners should not follow a stepped-care approach. Instead, therapy should be individualized, based on consideration of concurrent diseases, both cardiovascular and noncardiovascular.

Validation: All recommendations were graded according to the strength of the evidence and the consensus of all relevant stakeholders.

Sponsors: The Canadian Hypertension Society and the Canadian Coalition for High Blood Pressure Prevention and Control.

Special Supplement

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This article has been peer reviewed.

Hypertension remains a major public health issue, both in Canada and worldwide. Hypertension is a significant risk factor for cerebrovascular disease, coronary artery disease and congestive heart failure, as well as renal failure and peripheral vascular disease. Furthermore, this risk factor is reversible. There is now general agreement that the cardiovascular complications of hypertension can be effectively treated with both lifestyle modification and pharmacological therapy. In addition, in contrast to other risk factors for cardiovascular disease, the diagnosis of hypertension can be made noninvasively, and the resources for the diagnosis and monitoring of blood pressure are readily available.

Although the diagnosis and treatment of hypertension appear simple, this disease remains poorly managed. The Canadian Heart Health Survey reported that only about 50% of Canadians with hypertension are aware of their diagnosis, and only 16% have adequate blood pressure control — a dismal record, but one that is comparable with that seen in other industrialized countries.[1]

In the context of this increasingly appreciated shortfall in hypertension control rates, a critical re-evaluation of the Canadian recommendations for the treatment of hypertension was undertaken. This process, spearheaded by the Canadian Hypertension Society and the Canadian Coalition for High Blood Pressure Prevention and Control, was planned as a first step in the development of a new implementation strategy for improving blood pressure control and reducing cardiovascular disease related to hypertension in Canada.

The *1999 Canadian Recommendations for the Management of Hypertension* follow a process initiated in the early 1980s by the Canadian Hypertension Society and revisited in 1993.[2–6] These initial versions of the Recommendations were notable in that they represented one of the earliest attempts at evidence-based guidelines in hypertension, using strict criteria for the grading of evidence. Furthermore, the recommendations were, wherever possible, based on the identification of those therapies that not only effectively decreased blood pressure but also reduced the ultimate end points, namely, they decreased rates of hypertension-related cardiovascular complications. The current recommendations complete the current cycle of consensus conferences organized to review Canadian hypertension recommendations, including the *Report of the Canadian Hypertension Society Consensus Conference on the Management of Hypertensive Disorders in Pregnancy*[7–9] and the report entitled *Lifestyle Modifications to Prevent and Control Hypertension*.[10–16]

The task force for the development of the *1999 Canadian Recommendations for the Management of Hypertension* was organized at the direction of the Executive and Board of the Canadian Hypertension Society. A steering committee was struck comprising representatives from the Canadian Hypertension Society, the Canadian Coalition for High Blood Pressure Prevention and Control, Health Canada and the College of Family Physicians of Canada. The members of the steering committee reviewed and modified the consensus process used in 1993. In contrast to earlier efforts, the current Recommendations reflect a collaboration between the Canadian Hypertension Society and 9 partner organizations, including the Canadian Coalition for High Blood Pressure Prevention and Control, the Canadian Cardiovascular Society, the Canadian Diabetes Association, the Canadian Nurses Association, the Canadian Society of Nephrology, the Canadian Stroke Society, the College of Family Physicians of Canada, Health Canada and the Heart and Stroke Foundation of Canada.

Methods

Two chapter-writing committees were organized, one in diagnosis and the second in management, to review and grade the literature relating to hypertension management, particularly with regard to studies published since the last revision in 1993. Each member of the committee was assigned a specific topic area (see *Clinical problem solving*, page S18). Competing interest forms were completed by each participant in the process and reviewed by members of the steering committee.

Evidence pertaining to recommendations in each topic area was obtained as outlined below. This was evaluated by the individual assigned to each topic area. Based on this evaluation, each member of the committees prepared draft position papers on his or her assigned aspect of the diagnosis and pharmacological treatment of hypertension. These papers were circulated for review and critique to a broader panel of experts, designated by partner organizations. Each position paper was reviewed by members of a topic task force consisting of at least 2 other participants. Based on their comments, revisions of the position papers were made. A consensus conference was held in London, Ont., in June 1998 for a review of the documents and to develop draft recommendations. These draft recommendations were based on initial discussions within the task force groupings involved in the formulation/revision of the position papers and were subsequently presented to the entire assembly. Areas of disagreement were referred back to the individual task force groupings for ultimate representation to the entire assembly. The recommendations were subsequently circulated for voting to all participants in the consensus process. Those recommendations approved by more than 75% of the consensus panel were presented in open forum at a special symposium of the Canadian Hypertension Society, which was held in conjunction with the Canadian Cardiovascular Society meeting in Ottawa in October 1998. Areas of substantive comment were re-evaluated, and revised recommendations were recirculated for voting a second time and ultimate approval. The process was completed in April 1999. The recommendations approved through that process are described below.

As noted above, the development of these recommendations follows the tradition of the earlier versions in its critical analysis of the scientific literature and the grading of recom-

mendations based on strength of evidence. This process involved a systematic examination of the evidence and analysis of its quality. Articles were obtained using MEDLINE searches and examination of those areas reviewed by the Cochrane Collaboration. References cited in articles found through the literature search were also reviewed. Experts on the subject and the authors of some of the articles identified were asked to supply additional references, and panel members searched their personal files for relevant materials. The articles were classified according to study design and were reviewed individually. No other specific quality criteria were used to select or exclude articles. The evidence and recommendations were graded using the system previously used by the Canadian Hypertension Society[2–4] (Tables 1–5). Levels of evidence determined from review studies were not used in this process. It should be noted that the levels of evidence for studies were graded numerically (I–VI), whereas the grading system for recommendations is alphabetical, with A representing a recommendation based on one or more studies at level I and D representing evidence where the best evidence available is lower than level III and includes expert opinion.

What follows are the recommendations for the management of hypertension. It should be emphasized that the present set of recommendations is intended not only to guide the care of patients with hypertension but also as a technical document for the development of both clinical practice guidelines and a broader implementation strategy for improving blood pressure control and reducing cardiovascular complications. The recommendations are written from the perspective of optimal management as extrapolated from the best clinical trials evidence available. Neither public health policy nor economic considerations contributed to this process. In addition, these recommendations have not included consideration of individual patient preferences, which might have a significant impact on the implementation of a number of these recommendations, especially in the context of diagnosis and risk stratification.

Table 1: Levels of evidence for rating studies of diagnosis

I	a)	Independent interpretation of test procedure (without knowledge of result of diagnostic standard)
	b)	Independent interpretation of diagnostic standard (without knowledge of result of test procedure)
	c)	Selection of patients or subjects who are suspected of having, but are not known to have, the disorder of interest
	d)	Reproducible description of both the test and the diagnostic standard
	e)	At least 50 patients with and 50 without the disorder
II	Meets 4 of the criteria in I	
III	Meets 3 of the criteria in I	
IV	Meets 2 of the criteria in I	
V	Meets 1 of the criteria in I	
VI	Meets none of the criteria in I	

Table 2: Levels of evidence for rating studies of prognosis

I	a)	Inception cohort
	b)	Reproducible inclusion and exclusion criteria
	c)	Follow-up of at least 80% of subjects
	d)	Statistical adjustment for extraneous prognostic factors (confounders)
	e)	Reproducible descriptions of outcome measures
II	Inception cohort, but meets only 3 of the other criteria in I	
III	Inception cohort, but meets only 2 of the other criteria in I	
IV	Inception cohort, but meets only 1 of the other criteria in I	
V	Inception cohort, but meets none of the other criteria in I	

The diagnosis of hypertension

I Accurate measurement of blood pressure

Recommendations

1. The blood pressure of all adult patients should be

Table 3: Levels of evidence for rating studies of treatment, prevention and quality assurance

I	A randomized controlled trial (RCT) that demonstrates a statistically significant difference in at least one important outcome (e.g., survival or major illness)
OR	If the difference is not statistically significant, an RCT of adequate sample size to exclude a 25% difference in relative risk with 80% power, given the observed results
II	An RCT that does not meet the level I criteria
III	A nonrandomized trial with contemporaneous controls selected by some systematic method (i.e., not selected by perceived suitability for one of the treatment options for individual patients)
OR	Subgroup analysis of a randomized trial
IV	A before-after study or case series (of at least 10 patients) with historical controls or controls drawn from other studies
V	Case series (at least 10 patients) without controls
VI	Case report (fewer than 10 patients)

Table 4: Levels of evidence for rating review articles

I	a)	Comprehensive search for evidence
	b)	Avoidance of bias in the selection of articles
	c)	Assessment of the validity of each cited article
	d)	Conclusions supported by the data and analysis presented
II	Meets only 3 of the criteria in I	
III	Meets only 2 of the criteria in I	
IV	Meets only 1 of the criteria in I	
V	Meets none of the criteria in I	

assessed at all appropriate visits for the determination of cardiovascular risk and monitoring of antihypertensive treatment by health care professionals who have been specifically (re)trained to measure blood pressure accurately (grade C).
2. The use of a standardized measurement technique (Table 6) is recommended when assessing blood pressure for the determination of cardiovascular risk and monitoring of antihypertensive treatment (grade D).

Background

Accurate assessment of a person's blood pressure is necessary to determine whether patients are at increased risk of cardiovascular disease and would benefit from antihypertensive therapy. Surveys have demonstrated that blood pressure is not carefully assessed in clinical practice,[17,18] and this could lead to misclassification of cardiovascular risk. Accurate measurement of blood pressure requires particular attention to patient preparation, standardized measurement and accurate equipment.

II Criteria for diagnosis of hypertension and recommendations for follow-up

Recommendations

1. Patients presenting as a hypertensive urgency are diagnosed as hypertensive at their first (initial) visit and require immediate management (grade D).
2. If the initial (visit 1) blood pressure is high, then in the same session 2 readings should be taken, according to the recommended procedure for accurate blood pressure determination (Table 6), and further visits should be arranged for the patient (grade A).
3. Patients with target-organ damage can be diagnosed as hypertensive at/after visit 3 (grade B).
4. The search for target-organ damage, associated risk factors and exogenous causes of elevated blood pressure should proceed as follows (grade D):
   - i On the first visit, the patient should be questioned and the medical record reviewed for myocardial infarction, angina pectoris, transient ischemic attacks, cerebrovascular accident, peripheral arteriovascular insufficiency or renal insufficiency.
   - ii At visit 2, if the blood pressure is still elevated, a further history-taking and physical examination should be performed. Diagnostic tests should be arranged prior to visit 3.
5. If the blood pressure at visit 1 is between 140/90 and 180/105 mm Hg, at least 4 further visits are required to diagnose hypertension (since the greatest fall in blood pressure occurs between visit 1 and 2). These measurements can be performed over the next 6 months (grade B).
6. If, at the last diagnostic visit, the blood pressure is less

Table 5: Grading system for recommendations

A	The recommendation is based on one or more studies at level I
B	The best evidence available was a level II
C	The best evidence available was at level III
D	The best evidence available was lower than level III and included expert opinion

Table 6: Recommended technique for measuring blood pressure

i	Measurements are preferably taken with a mercury manometer, but a recently calibrated aneroid manometer or a validated and recently calibrated electronic device can be used. Aneroid devices and mercury columns need to be clearly visible at eye level.
ii	Choose a cuff with an appropriate bladder width (bladder width X 2.5) +/– 4 cm = the arm circumference.
iii	Place the cuff so that the lower edge is 3 cm above the elbow crease and the bladder is centred over the brachial artery. The patient should be resting comfortably for 5 minutes in the seated position with back support. The arm should be bare and supported with the antecubital fossa at heart level. There should be no talking, and the patient's legs should not be crossed. Blood pressure also should be assessed after 2 minutes' standing and at times when the patient complains of symptoms suggestive of postural hypotension.
iv	Increase the pressure rapidly to 30 mm Hg above the level at which the radial pulse is extinguished (to exclude the possibility of auscultatory gap).
v	Place the head of the stethoscope gently but firmly over the brachial artery.
vi	Open the control valve so that the rate of drop in the vicinity of the systolic and diastolic level is 2 mm Hg per beat.
vii	Read the systolic level — the first appearance of a clear tapping sound (phase I Korotkoff) — and the diastolic level — the point at which the sounds disappear (phase V Korotkoff). Record the blood pressure to the closest 2 mm Hg on the manometer (or 1 mm Hg on electronic devices), as well as the arm used and whether the patient was supine, sitting or standing. Record the heart rate. The seated blood pressure is used to determine and monitor treatment decisions. The standing blood pressure is used to check for postural hypotension, which, if present, may modify the treatment.
viii	If Korotkoff sounds persist as the level approaches 0 mm Hg, then the point of muffling of the sound is used (phase IV) to indicate the diastolic pressure.
ix	In the case of arrhythmia, additional readings may be required to estimate the average systolic and diastolic pressure. Isolated extra beats should be ignored. Note the rhythm and pulse rate.
x	Leaving the cuff partially inflated for too long will fill the venous system and make the sounds difficult to hear. To avoid venous congestion, it is recommended that at least one minute should elapse between readings.
xi	Blood pressure should be taken at least once in both arms. If one arm has a consistently higher pressure, that arm should be used subsequently.

than 140/90 mm Hg and the patient has no evidence of target-organ damage or associated risk factors, the patient should be assessed yearly (grade D). Such patients are at low risk (grade A) and should not be labelled hypertensive (grade D)
7. Follow-up of patients on lifestyle modification (nonpharmacological treatment) should be at 3- to 6-month intervals (grade D).
8. Follow-up of patients on antihypertensive drug treatment:
   i Patients should be seen monthly until 2 blood pressure readings are below their target. (grade D).
   ii Shorter intervals between visits will be needed for symptomatic patients, those with severe hypertension, intolerance of antihypertensive drugs or those with target-organ damage (grade D).
   iii Once target blood pressure has been reached, patients should be seen at 3- to 6-month intervals (grade D).

Background

The diagnosis of elevated cardiovascular risk due to high blood pressure can be made immediately in the presence of specific target-organ damage (expert opinion). In general, the closer an individual's blood pressure is to normal, the greater the risk of misclassification.[19–21] More readings, at more frequent intervals, are required to establish a diagnosis of hypertension in those without target-organ damage and in those whose blood pressure is close to the normal blood pressure range. For those whose blood pressure at visit 1 is between 90 and 95 mm Hg, 7% to 24% will be misclassified as hypertensive after 4 visits.[20,21]

III Routine laboratory tests for the investigation of all patients with hypertension

Recommendations

Routine laboratory tests for the investigation of all patients with hypertension (grade D):
1. Urinalysis
2. Complete blood cell count
3. Blood chemistry (potassium, sodium and creatinine)
4. Fasting glucose
5. Fasting total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides
6. Standard 12 ECG

Background

There is little evidence on which to base recommendations for laboratory testing. However, to determine the risk of cardiovascular disease in patients and to examine for secondary hypertension, laboratory testing is essential. The recommended tests have been based on expert opinion.

IV Home blood pressure monitoring

Recommendations

1. Specific roles for home blood pressure monitoring in selected patients include the following:
   i The use of home blood pressure monitoring on a regular basis should be considered in patients suspected to be noncompliant under close clinical supervision and among diabetic patients (grade B noncompliant patients, grade D diabetic patients).
   ii When using home monitoring to assess patients for "white-coat" hypertension, further assess those identified to have white-coat effect using ambulatory blood pressure monitoring, if available.
2. Patients should be advised to purchase and use only home blood pressure monitoring devices that have met the standards of the Association for Medical Instrumentation or the British Hypertension Society, or both (grade D).
3. Home blood pressure values of approximately 135/83 mm Hg or greater should be considered elevated (grade B).
4. If patients measure their blood pressure at home, health care professionals should ensure that patients have adequate training in measuring their blood pressure and adequate information about interpreting these readings (grade D).
5. The accuracy of all individual patients' devices (especially electronic devices) and techniques (especially acoustic devices) must be regularly checked against a device of known calibration, for example, a mercury-column sphygmomanometer (grade D).

Background

Home blood pressure monitoring can provide additional useful information for hypertension management. However, there is insufficient evidence at present to recommend home blood pressure monitoring for routine clinical use in the evaluation of all patients with hypertension. The use of home blood pressure monitoring can increase patient compliance in those suspected of being noncompliant[22,23] and can increase compliance among diabetic patients.[24] There is a lack of data on the prognosis of patients with different levels of blood pressure on home monitoring. The existing data strongly suggest that levels of blood pressure at home are lower than those in the office,[25–27] and values above 135/83 mm Hg should be considered elevated.[25–28] Patients measuring blood pressure at home should be trained by a qualified health care professional and should be provided with adequate informa-

tion to interpret their home blood pressure values.[29] Very few automated home blood pressure monitoring devices meet rigorous standards for accuracy and reliability,[30] and many devices become less accurate over time.

V Ambulatory blood pressure monitoring

Recommendations

1. Physicians should use only ambulatory blood pressure monitoring devices that have been validated independently using established protocols (grade A).
2. A decision to withhold drug therapy, based upon the ambulatory blood pressure, should take into account normal values for 24 hours and awake ambulatory blood pressure, as outlined below (grade B).
3. Ambulatory blood pressure monitoring should be considered for untreated patients whenever an office-induced increase in blood pressure is suspected, including patients with mild-to-moderate blood pressure elevations in the clinic, without target-organ damage (grade A).
4. Ambulatory blood pressure monitoring should be considered for treated patients suspected of having an office-induced increase in blood pressure, including those with apparent resistance to drug therapy, symptoms suggestive of hypotension and fluctuating office blood pressure readings (grade B).
5. Changes in nocturnal blood pressure should be taken into account in any decision to withhold drug therapy based upon ambulatory blood pressure (grade A).

Background

The Association for Medical Instrumentation[31] and the British Hypertension Society[32] have developed protocols for independently validating blood pressure measurement devices. Normal values for ambulatory blood pressure monitoring have been defined based on their equivalence to office blood pressure readings. One outcome study has identified a mean 24-hour ambulatory blood pressure greater than 134/78 mm Hg as being predictive of increased total and cardiovascular mortality.[33] A second outcome study has defined normal daytime ambulatory blood pressure as less than136/87 mm Hg for men and less than131/86 mm Hg for women.[34] People with normal blood pressure on 24-hour monitoring have a prognosis similar to those with normal office blood pressure. Blood pressure usually decreases 10% to 20% during sleep. In those whose blood pressure does not dip 10%, there is a poorer cardiovascular prognosis.[34] To facilitate the clinical use of recommendations, the American Society of Hypertension has suggested that daytime ambulatory blood pressure less than 135/85 mm Hg be considered normal.[35] Twenty percent to 40% of patients with elevated office blood pressures will have normal blood pressures during 24-hour ambulatory monitoring.[17,35,36] Patients receiving long-term antihypertensive therapy may demonstrate a difference between office and ambulatory blood pressure values. Patients whose drug therapy was adjusted on the basis of ambulatory blood pressure monitoring required fewer drugs, but they had a similar total cost of health care and ambulatory blood pressure after 6 months, compared with patients whose blood pressure treatment was adjusted based on office readings.[37]

VI Role of echocardiography in hypertension

Recommendations

1. Routine echocardiographic evaluation of all hypertensive patients is not recommended (grade D).
2. Echocardiographic assessment of left ventricular mass, as well as of systolic and diastolic left ventricular function, is recommended for hypertensive patients suspected of having left ventricular dysfunction or coronary artery disease (grade D).
3. Echocardiography should not be used to track the therapeutic regression of left ventricular hypertrophy (LVH) (grade D).

Background

Measuring of ventricular masses by echocardiography is valid, serially reproducible and clinically applicable but has high interstudy variability, even with meticulous attention to technique.[38,39] Furthermore, there are no data from prospective trials examining the outcome and cost-effectiveness of routine echocardiography. Since LVH is an important independent risk factor for cardiovascular complications in hypertensive patients, its detection may have an impact on patient management. Thus, echocardiography is justifiable in selected cases. Reproducibility of echocardiographic ventricular mass measurements in the clinical setting is not sufficiently reliable for tracking therapeutic regression of ventricular hypertrophy in a given patient.[39,40] Recent Canadian guidelines have been published for the echocardiographic assessment and reporting of left ventricular mass and diastolic dysfunction.[41,42]

The pharmacological treatment of hypertension

I Indications for drug treatment

Recommendations

1. Drug therapy for hypertension should be strongly considered in all adults under 60 years of age with sustained diastolic blood pressure of 90 mm Hg or higher (grade A).

Drug therapy should be considered for adults less than 60 years of age with isolated systolic hypertension in which systolic blood pressure is greater than 160 mm Hg,

particularly in those with target-organ damage, concomitant diseases such as diabetes mellitus or other independent cardiovascular risk factors (grade D).

   i Drug therapy should be prescribed for all hypertensive adults under 60 years of age with target-organ damage related to uncontrolled hypertension (grade C) or one of the following diseases: diabetes mellitus, renal parenchymal disease or cardiovascular disease (grade C). (Please refer to specific sections of this report for details.)
   ii The presence of other independent cardiovascular risk factors such as greater age, male sex, being postmenopausal, black race, elevated systolic blood pressure, continued cigarette smoking, glucose intolerance or abnormal blood lipid profile should strongly influence the decision to initiate drug therapy (grade C). Other factors including a strong family history of hypertension or premature cardiovascular disease, increased body mass index or truncal obesity, and sedentary lifestyle should also be taken into account (grade D).

2. Irrespective of any other factors, drug therapy for hypertension should be prescribed for all adults under 60 years of age with diastolic blood pressure readings averaging 100 mm Hg or higher (grade A).
3. For all adults over 60 years of age, drug therapy should be prescribed for systolic blood pressures of 160 mm Hg or higher (grade A) or for diastolic blood pressures of greater than 105 mm Hg (grade A).

Background

The present version of the recommendations for hypertension management emphasizes the importance of cardiovascular risk assessment when making treatment decisions. It is well known that the risk of cardiovascular disease in hypertensive patients with identical blood pressure readings can vary more than 10-fold depending on the presence of other cardiovascular risk factors, hypertension-related complications, cardiovascular diseases or other illnesses.[43] The strongest considerations should be made for those at the highest risk of cardiovascular complications based on age, sex, racial group, tobacco use, dyslipidemia, etc. The use of blood pressure threshold alone to make treatment decisions should be reserved for those hypertensive patients at lowest risk (i.e., premenopausal women without other risk factors). These recommendations are based on a re-evaluation of preexisting information from clinical trials, overviews and observational studies, as there are no new level I clinical trials of antihypertensive drug therapy in which active treatment was assigned based on absolute risk of cardiovascular disease. The impetus to base treatment on absolute overall risk level (or "numbers needed to treat" to prevent a clinical event) relates principally to efficiencies in managing individual patients.[44] This approach, however, discounts the value of preventing progression of disease processes such as LVH, vascular remodelling and atherosclerosis and development of more severe blood pressure levels. This is particularly important in the low-risk groups who are more likely to be young and female, in whom death or severe morbid events result in more years of life lost or disability days. This treatment strategy also ignores the preferences of potential recipients of treatment that may vary substantially from the preferences of those setting policy.[45] For indications for treatment in special population groups (i.e., for patients with diabetes or renal disease), see specific section for details.

II Choice of therapy in adults younger than 60 years of age with uncomplicated hypertension

Recommendations

1. Initial therapy should be monotherapy with a thiazide diuretic, preferably at a low dose, a β-adrenergic antagonist or an angiotensin-converting-enzyme (ACE) inhibitor (grade A). If the response is inadequate or there are adverse effects, substitute another drug from the initial drug therapy group (grade D).
2. Combination therapy, either with a thiazide diuretic and a β-adrenergic antagonist or with a thiazide diuretic and an ACE inhibitor, should be used if there is only a partial response to monotherapy (grade A).
3. If blood pressure is still not controlled, or there are adverse effects, try other classes of antihypertensive drugs (calcium-channel blockers, angiotensin II receptor antagonists, α-adrenergic antagonists or centrally acting agents) either as monotherapy or in combination (grade D). Consider possible reasons for a poor response to therapy, such as noncompliance, secondary causes of hypertension or interactions between prescribed treatment and diet or other drugs (grade D).

Background

The recommendations for preferred drug therapy for uncomplicated hypertension are based on clinical trial evidence (level 1) in hypertensive patients in whom agents have been shown to (1) effectively lower blood pressure and (2) reduce cardiovascular events. In younger hypertensive patients (less than 60 years of age), such data exist for diuretics, β-adrenergic antagonists[4] and ACE inhibitors,[46] but not for calcium-channel blockers. In the absence of such data in this patient population, calcium-channel blockers are recommended as alternative agents for the treatment of hypertension that cannot be controlled with preferred therapy. Drug cost, which may affect public health policy decisions, was not taken into account in making these recommendations.[47]

It should be re-emphasized that regarding the prescription of lifestyle modifications, which have an important role in hypertension management, readers are referred to our recently published recommendations.[10–16]

III Choice of therapy in adults older than 60 years of age with uncomplicated hypertension

Recommendations

1. For uncomplicated hypertension without contraindication, the preferred therapy in hypertensive patients over the age of 60 years consists of low-dose thiazide diuretics (grade A) and long-acting dihydropyridine calcium-channel blockers antagonists (grade A).
2. Although β-adrenergic antagonists may be useful as adjunctive therapy in elderly patients taking diuretics, they are not recommended as first-line therapy (grade A).
3. An ACE inhibitor (grade B) or angiotensin II receptor antagonist (grade D) should be considered as alternative therapy when diuretics or calcium-channel blockers are ineffective, contraindicated or not tolerated.
4. Centrally acting agents and α-adrenergic antagonists are effective for decreasing blood pressure and reducing cardiovascular events (grade B). However, cognitive impairment resulting from therapy with methyldopa, postural hypotension from α-adrenergic antagonists (e.g., prazosin, terazosin and doxazosin), drowsiness, rebound hypertension and depression from reserpine may limit the use of these otherwise effective antihypertensives in older people.

Background

Failure to treat isolated systolic hypertension in the elderly represents an important gap in health care, since hypertension is more prevalent in the elderly. Furthermore, treatment of isolated systolic hypertension in the elderly is much more effective (i.e., the number needed to treat is much smaller) than treating diastolic hypertension in younger patients: stroke is reduced by half, myocardial infarction by 40%[48] and Alzheimer's dementia by half.[49] Systolic pressure continues to rise with age, whereas diastolic pressure levels off at the age of 55 years and then declines with age. Furthermore, vascular complications correlate more strongly with systolic than with diastolic blood pressure.[1,50]

It should be noted that the basis of the recommendations for therapy in older hypertensive patients comes, in the main, from large, well-conducted, randomized controlled trials that have been reported.[48,49,51–59] These studies included relatively healthy elderly people generally between the ages of 60 and 84 years. Thus, the generalizability of recommendations to the frail elderly and those older than 84 years of age may be limited. (For newly diagnosed hypertension in patients older than 84 years, investigation and therapy should be cautious and individualized.) As in younger patients, the recommendations for preferred therapies were based on consideration of those drugs that have been shown (in level I studies) to reduce both blood pressure and blood pressure–related complications. This has been most clearly demonstrated with the thiazide diuretics[48] and longer-acting dihydropyridine calcium-channel blockers.[51]

IV Goal of therapy

Recommendation

1. The diastolic blood pressure treatment goal is a pressure level of less than 90 mm Hg (grade A). For systolic blood pressure, the goal is a pressure level of less than 140 mm Hg (grade D).

Background

Previous versions of this report did not include specific recommendations regarding the goals of treatment. The recommendation for target diastolic blood pressure is based on both previously evaluated trials[4] and the results of the recently published HOT study that found no significant between-group differences in cardiovascular events in subjects randomized to a diastolic blood pressure treatment goal of less than 90, less than 85 or less than 80 mm Hg.[60] The study also showed that there is no harm caused by further blood pressure lowering and that the subgroup with diabetes mellitus may even benefit from a lower diastolic blood pressure threshold for initiating drug treatment, as well as a lower treatment goal (see section VII).

V Hyperlipidemia

Recommendation

1. In the setting of dyslipidemia, therapy for hypertension should follow the recommendations for uncomplicated hypertension or for patients with other concurrent risk factors or diseases (grade B).

Background

Patients with abnormal lipid levels are at increased risk of cardiovascular events that can be reduced with a reduction in LDL cholesterol. Treatment should be in accordance with current guidelines.[61]

Many studies have continued to be published on the effects of various antihypertensive drugs on serum lipids, including the adverse effects of high doses of thiazide diuretics and β-adrenergic antagonists and the beneficial effects of α-adrenergic antagonists. They have generally been of relatively short duration. Adverse effects on serum lipids of various antihypertensives and changes in

serum lipids have not been accompanied by evidence of altered incidence of atherosclerotic complications. Notably, the longest and largest study, the Treatment of Mild Hypertension Study (TOMHS)[62] did not demonstrate sustained adverse effects on lipids of representatives of the 5 major antihypertensive classes (acebutolol, amlodipine, chlorthalidone, doxazosin and enalapril), although there were small differences among these agents. Thus, the recommendations reflected the view that the choice of antihypertensive therapy in dyslipidemic patients should not be inordinately affected by consideration of their lipid status.

VI Cigarette smoking

Recommendation

1. The benefits of β-adrenergic antagonist therapy in hypertensive smokers remain uncertain. Thus, β-adrenergic antagonists are not recommended for hypertensive patients who smoke, in the absence of target-organ damage or concurrent cardiovascular disease (grade C).

Background

Post-hoc subset analysis of several intervention trials[59,63–65] has provided evidence in hypertensive patients who smoke for the absence of benefits from treatment with β-antagonists against coronary events. Thus, in patients with uncomplicated hypertension who smoke, other first-line agents should be considered preferentially (i.e., diuretics or ACE inhibitors)

VII Diabetes

Recommendations

1. Hypertension in people with diabetes (blood pressure greater than 140/90 mm Hg) should be treated to obtain target blood pressure lower than 130/80 mm Hg (grade C).
2. People with diabetes and hypertension with blood pressure of 130/80 to 139/89 mm Hg and target-organ damage should be treated to obtain a target blood pressure lower than 130/80 mm Hg (grade D).
3. For patients with diabetes who have hypertension without overt nephropathy and are under 60 years of age, preferred therapy is either an ACE inhibitor or a cardioselective β-adrenergic antagonist (grade A).
4. Second-line therapy includes low-dose thiazide diuretics (grade B), long-acting calcium-channel blockers (grade B) and α-adrenergic antagonists (grade C). α-adrenergic antagonists and centrally acting antihypertensive agents should be used with caution in the presence of autonomic neuropathy (grade C).
5. Preferred therapy for patients with diabetes, hypertension and overt nephropathy (albuminuria greater than 300 mg/day) is an ACE inhibitor (grade A).
6. When an ACE inhibitor causes adverse effects, an angiotensin II receptor antagonist may be substituted (grade D).
7. Preferred therapy for patients with diabetes and isolated systolic hypertension who are over 60 years of age is either low-dose thiazide diuretics or long-acting dihydropyridine calcium-channel blockers (grade C).
8. If monotherapy with first-line agents is ineffective, contraindicated or associated with adverse side effects, the following should be considered:
   - i A long-acting calcium-channel blocker may be combined with an ACE inhibitor (grade B). A low-dose thiazide diuretic may be added to an ACE inhibitor without adversely affecting microalbuminuria (grade B).
   - ii For patients with renal insufficiency, a loop diuretic may be required to control volume and blood pressure (grade C).
   - iii Indapamide may be substituted for low-dose thiazide as it may reduce microalbuminuria (grade C).

Background

The coexistence of diabetes with hypertension has a significant multiplier effect on the risk of both the macrovascular complications (i.e., cerebrovascular, coronary and peripheral vascular disease) and microvascular complications (i.e., retinopathy and nephropathy) associated with these diseases.[66–69] This has important implications for selecting thresholds for instituting drug therapy and target blood pressures with treatment.[70] The recommendation to lower the blood pressure thresholds for the initiation of drug therapy for patients with diabetes and demonstrated target-organ damage is based on studies of the treatment of patients with both insulin-dependent and non-insulin-dependent diabetes and overt nephropathy (i.e., proteinuria or renal insufficiency, or both) who, on average, had high normal blood pressures.[71–80] Therapy with ACE inhibitors was associated with reductions in the renal complications common to both hypertension and diabetes. The lower target for blood pressure control in patients with diabetes follows from several lines of evidence: (1) the demonstrated improvement in outcomes with aggressive blood pressure lowering in the UKPDS 38 study[81] and (2) the reduced complication rate in those patients with diabetes enrolled in the HOT study [60] assigned to the group whose goal diastolic blood pressure was lower than 80 mm Hg.

As is the case for patients with uncomplicated hypertension or other concurrent diseases or risk factors, the recommendations for first-line antihypertensive therapy for patients with diabetes are based on consideration of those drugs that have been shown to (1) lower blood pressure effectively and (2) to reduce hypertension-related complications. For patients with diabetes and evidence of target-

organ damage, this has been most clearly demonstrated for the ACE inhibitors, hence, the recommendation of this class of drug as first-line therapy (as cited above). Furthermore, both the CAPPP[46] and HOPE studies (S Yusuf: personal communication) demonstrated that ACE inhibitors reduce the incidence of diabetes (presumably by reducing the rate of progression from lesser grades of insulin resistance). In the absence of nephropathy, β-adrenergic antagonists are recommended as alternative first-line therapy, given their comparable effects in reducing hypertension-related complications in the UKPDS 38 study.[81] For those patients over the age of 60 years with diabetes and systolic hypertension, the recommendations for first-line therapy follow those for uncomplicated systolic hypertension, namely, either a diuretic or long-acting dihydropyridine calcium-channel blocker. These recommendations are based, in part, on the SHEP[82] and Syst–Eur studies,[51,83] where patients with diabetes demonstrated a beneficial effect of therapy comparable with that in the overall study population (Table 7).

VIII Ischemic heart disease

Recommendations

1. For patients with stable angina and hypertension, β-adrenergic antagonists are preferred as initial therapy (grade D).
2. Alternative therapies would include long-acting calcium-channel blockers (grade B). Short-acting calcium-channel blockers should not be used (grade C).
3. Patients with hypertension and a recent myocardial infarction should be treated with either β-adrenergic antagonists, ACE inhibitors or both. Both classes of drug protect against reinfarction and death (grade A).
4. Alternative therapies would include verapamil (grade A) and diltiazem (grade C), but only in the setting of normal left ventricular function.

Background

There have been no large, randomized controlled trials designed to demonstrate a statistically significant difference in an important outcome such as survival in patients with stable angina and hypertension treated with medications that lower blood pressure. The principal goal in this literature has been the demonstration that ischemia has been suppressed. It should be noted that the grading in this section, unless stated otherwise, is based on the level of evidence for demonstrating reduction in coronary artery disease, mortality or serious morbidity (e.g., reduction in rates of myocardial infarction as opposed to reduction in the frequency of angina).

Table 7: Preferred antihypertensive therapies for patients with diabetes

Albuminuria	Preferred therapy	Grade
> 300 mg/day	ACE inhibitor	A
< 300 mg/day	ACE inhibitor	A
	β-Adrenergic antagonist	A

Note: For patients with diabetes who are over 60 years of age and have isolated systolic hypertension: either low-dose thiazide diuretics or long-acting dihydropyridine calcium-channel blockers (grade C).

Most randomized clinical trials or treatments for ischemic heart disease (as well as for the other cardiovascular diseases listed below) have studied drugs with antihypertensive properties, but they have not specifically addressed their effect in hypertensive patients with these disorders.[84–91] Because there would be no biological rationale for the effects of these drugs being qualitatively different in normotensive and hypertensive populations, evidence for the benefit of therapy on important outcomes, overall, has been extrapolated to the hypertensive subset of these study patients.

Tachycardia appears to be an important determinant of coronary risk in hypertension, but the hypothesis that lowering heart rate by treatment will have a greater effect on mortality than blood pressure reduction alone has not been formally tested.[92]

IX Systolic dysfunction

Recommendations

1. In patients with hypertension and systolic dysfunction, ACE inhibitors are recommended for initial therapy (grade A). Diuretics are recommended as additional therapy (grade A for thiazide diuretics, grade D for loop diuretics).
2. A combination of hydralazine and isosorbide dinitrate (grade A) or an angiotensin II receptor antagonist (grade A in patients older than 65 years of age) is recommended as an alternative therapy.
3. For patients with left ventricular systolic dysfunction who remain hypertensive despite optimal doses of ACE inhibitors or alternative first-line therapies, additional therapies would include β-adrenergic blockade with either carvedilol (grade A), or metoprolol (grade A) or the long-acting dihydropyridine calcium-channel blockers amlodipine (grade A) or felodipine (grade B).

Background

Hypertension persisting after the development of heart failure is associated with more frequent adverse outcomes such as hospitalization.[93] The treatment of hypertension in patients with congestive heart failure should generally include ACE inhibitors[91] and diuretics, if salt and water retention requires therapy. The ACE inhibitors are specifically recommended for the treatment of congestive heart failure with or without hypertension and are generally administered in combination with

digoxin and furosemide.[94] The RALES study[95] reported a significant mortality benefit from the addition of the aldosterone antagonist and diuretic, spironolactone, to ACE inhibitors, diuretics and digoxin in congested patients. Hydralazine, combined with isosorbide dinitrate, has been shown to be effective in the treatment of heart failure and may be considered if ACE inhibitors are contraindicated or not tolerated.[96] Angiotensin II receptor antagonists may also be considered for this purpose.[97] Several β-adrenergic antagonists have been shown to have mortality benefit in New York Heart Association class II or III patients with congestive heart failure.[98–101] Of these, metoprolol and bisoprolol are β_1-adrenergic antagonists, whereas carvedilol is a nonselective β-adrenergic antagonist and also blocks α_1-adrenoceptors. There is a limited role for calcium-channel blockers in this condition.[102,103] β-adrenergic antagonists should be introduced only in appropriate patients and, initially, at very low doses with close monitoring and graded uptitrations as tolerated. Consultation with a specialist familiar with the application of these drugs for this purpose is recommended.

X Peripheral vascular disease

Recommendations

1. For hypertensive subjects with peripheral vascular disease and no other risk factors or target-organ disease, the therapeutic recommendations follow those for uncomplicated hypertension (grade D) with the following considerations:
   - i β-adrenergic antagonists, verapamil or ACE inhibitors do not worsen the symptoms of peripheral vascular disease. β-adrenergic antagonists may be used in mild-to-moderate disease but may aggravate the symptoms of severe disease (grade B).
   - ii The use of ACE inhibitors may cause renal impairment in those patients with underlying renal artery stenosis (grade B).
2. In patients with Raynaud's phenomenon, vasodilators, including α-adrenergic antagonists, calcium-channel blockers and ACE inhibitors/angiotensin II receptor antagonists, may be of benefit (grade B), in preference to β-adrenergic antagonists (grade B).

Background

The symptoms of severe peripheral vascular disease may be exacerbated by the use of β- adrenergic antagonists, especially of the nonselective type. However, β-adrenergic antagonists may be used in most patients with mild peripheral vascular disease accompanied by intermittent claudication. In a short-term study, verapamil has also shown symptomatic benefit in the treatment of patients with moderate intermittent claudication.[104] Angiotensin-converting-enzyme inhibitors can be provided to those patients intolerant of β-adrenergic antagonists, but renal function must be monitored carefully in patients at high risk of renal vascular disease.[105,106] Patients with hypertension and coexisting collagen vascular disease with Raynaud's phenomenon may benefit from treatment with vasodilators.[107,108]

XI Arrhythmias and conduction disturbances

Recommendations

1. β-adrenergic antagonists, or the nondihydropyridine calcium-channel blockers, can be used for the control of the ventricular response to atrial fibrillation or to attempt suppression of specific supraventricular tachycardias in hypertensive patients with these arrhythmias (grade B).
2. In hypertensive patients with sinus node disease or atrial-ventricular conduction disorders, β-adrenergic antagonists, verapamil, diltiazem, clonidine and methyldopa should be avoided (grade D).

Background

Of the various antihypertensive agents available at present for the maintenance of sinus rhythm in patients predisposed to atrial fibrillation or paroxysmal supraventricular tachycardia, sotalol, which has β-adrenergic antagonist and class III antiarrhythmic properties, may be on balance the most efficacious, but this should be used with caution in patients with chronic renal insufficiency.[109] If a second antihypertensive is required, diuretics should be avoided, as this combination places such patients at increased risk of ventricular tachycardias, such as torsades de pointes.[110]

XII Cerebrovascular disease

A major goal in the treatment of hypertension is the prevention of stroke. Whether blood pressure should be lowered as part of the management of acute stroke has not been established.[111] During the recovery phase following cerebral infarction, ACE inhibition can lower systemic blood pressure without affecting cerebral blood flow.[112] Hypertensive patients who have had a stroke are at a high risk of recurrence, which can be reduced by antihypertensive therapy.[113] The choice of antihypertensive therapy for patients with hypertension and cerebrovascular disease should be based on consideration of other concurrent diseases or risk factors.

XIII Left ventricular hypertrophy

Recommendation

1. The reversal of LVH by antihypertensive therapy may lower the rate of subsequent cardiovascular morbid

events (grade C). Most antihypertensive drugs reduce LVH over a 6-month treatment period, in proportion to the reduction in blood pressure (grade A); the exceptions are arteriolar vasodilators, such as hydralazine or minoxidil, which can increase it (grade C). At present, there is insufficient evidence to base initial therapy on the reported effects of specific drugs on LVH.

Background

Left ventricular hypertrophy is commonly associated with hypertension and is an independent risk factor and predictor for cardiovascular disease and sudden death.[114] As of July 1995, there were 39 clinical trials published in English of the effect of monotherapy (with diuretics, β-adrenergic antagonists, calcium-channel blockers, ACE inhibitors or placebos) on left ventricular mass index, as determined by echocardiography. All trials employed a double-blind, randomized controlled parallel-group study design. A meta-analysis of these studies identified a significant relationship between the decrease in left ventricular mass achieved and both the duration of therapy and the reduction in systolic (but not diastolic) blood pressure.[115] Decreases in both posterior and septal wall thickness were significantly related to reductions in both systolic and diastolic blood pressure. Patients assigned to each drug class were well matched with respect to age, but not duration of treatment. After adjustment for duration of treatment, left ventricular mass decreased 13% with ACE inhibitors, 9% with calcium-channel blockers, 7% with diuretics and 6% with β-adrenergic antagonists. The ACE inhibitors reduced left ventricular mass and wall thickness more than β-adrenergic antagonists ($p < 0.05$ for both). The effects of the other 2 classes of drug were intermediate and not significantly different from that of the ACE inhibitors. A similar pattern emerged for changes in posterior wall thickness.

Several caveats need to be mentioned regarding this meta-analysis. No published studies of other drug classes, such as α-adrenergic antagonists, centrally acting agents, vasodilators or angiotensin II receptor antagonists, were available for analysis or, if published, failed to meet the authors' inclusion criteria. These authors subsequently conducted their own small study in which treatment with an α-adrenergic antagonist and a β-adrenergic antagonist caused similar and significant reductions in left ventricular mass index.[116] Trials finding no differences between drug class may never have appeared in the literature. The total number of drug-treated patients in this meta-analysis was only 1205 and placebo-treated patients, 189. The mean duration of treatment was only 25 weeks. The effect of drug treatment on left ventricular mass index was not significantly different from the effect of placebo ($p < 0.08$). The TOHMS study of over 800 patients [117] was not included in this analysis. The reason given for this decision was that the nonpharmacological interventions applied in that study (weight reduction, restriction of salt intake and intensive physical exercise) reduced blood pressure and left ventricular mass so successfully that no information could be derived about the effect of various antihypertensive agents on LVH. Left ventricular diastolic diameter and changes in this variable were reported in less than 50% of the treatment arms. Thus, the authors could not determine whether the decrease in left ventricular mass was due to a decrease in wall thickness, a decrease in internal diameter or both.

Subsequently, the Veterans Affairs Co-operative Study Group reported on the left ventricular mass of 1105 patients (58% black) who were randomly allocated to monotherapy with one of the following antihypertensive drugs: atenolol, captopril, clonidine, diltiazem, hydrochlorothiazide or prazosin. They were then followed for 1 year.[118] Significant reductions in adjusted left ventricular mass were reported for patients in the highest pretreatment tertile (> 350 g) if they were treated with hydrochlorothiazide (-43 g), captopril (-9 g) and atenolol (-28 g), but not with the other 3 drugs. In all 3 groups, reductions in left ventricular mass were due to decreases in wall thickness rather than internal diameter. However, only approximately 20% of the randomized patients had echocardiographic comparisons performed at 1 year. Of the prescribed drugs, only captopril achieved a significant reduction in left ventricular mass (-15 g) prior to stratification of patients into these 3 subgroups. A 3-year follow-up of 94 elderly patients with isolated systolic hypertension treated randomly with chlorthalidone or placebo as part of the SHEP study[48] documented a significant 13% reduction in left ventricular mass index in actively treated patients compared with a 6% increase in the group assigned to placebo.[119]

Although ACE inhibitors might have greater potential to reverse LVH, there is no evidence from randomized controlled trials that the regression in left ventricular mass associated with this particular class of drug is followed by a reduced incidence of cardiovascular events, including sudden death. When compared with 145 patients with essential hypertension without complications who had been treated with a variety of drugs alone or as combination therapy, but with no change or increase in left ventricular mass, 285 similarly treated patients with a serial reduction in left ventricular mass had significantly fewer cardiovascular morbid events over an average follow-up period of 3.2 years.[120] Although these are highly encouraging data, those with regression also had more successful lowering of their blood pressure. Therefore, the consensus view was that, at present, there is no support for a particular agent to be chosen for initial therapy because of its ability to prevent or reverse LVH.

XIV Renal disease

Recommendations

1. For patients with nondiabetic renal disease, target

blood pressure is 130/80 mm Hg (mean arterial pressure [MAP] 98) (grade C).
2. For patients with proteinuria that is greater than 1 g/day, target blood pressure is lower than 125/75 mm Hg (MAP 92) (grade C).
3. For patients with hypertension and renal disease, preferred initial therapy is with an ACE inhibitor (grade A).
4. Diuretics are recommended as additional antihypertensive therapy, since patients with renal insufficiency usually have difficulty with sodium balance (grade D).
5. Dihydropyridine calcium-channel blockers are recommended as alternative therapy for renoprotection in patients with nondiabetic renal disease (grade B).

Background

The rate of deterioration of renal function appears to correlate directly with blood pressure, most particularly with diastolic blood pressure over 90 mm Hg.[121–124] There is an important interaction of urinary protein excretion and blood pressure with the result that those patients with high urinary protein excretion are at high risk of renal failure, as are those patients with high blood pressure; patients with both high urinary protein excretion and high blood pressure are at the greatest risk of renal failure. Treatment for high blood pressure should be initiated when diastolic blood pressure is greater than 90 mm Hg.

The MDRD (Modification of Diet in Renal Disease) trial[124,125] assessed the effect of protein-restricted diets and different target blood pressures in patients with nondiabetic renal disease and a glomerular filtration rate of 15 to 55 mL/min, with serum creatinine levels of 106 to 616 mol/L. For patients with urinary protein excretion of more than 3 g/day, control of MAP to 92 mm Hg or less (125/75) slowed down deterioration of renal function. For the patients with urinary protein excretion of less than 3 g/day, a MAP of 98 (130/80) was associated with a reduced decline in GFR.

Two recent prospective studies[126–128] have confirmed the earlier findings of smaller studies[129,130] that ACE inhibitors slow down the deterioration of renal function better than conventional therapy.[131] These studies showed that the risk of developing renal failure was reduced by more than 50% in patients treated with an ACE inhibitor. The long-term extension of the REIN study (a study of the effect of ramipril) was continued and those patients in the placebo group were crossed over to receive ramipril. Long-term treatment with ramipril virtually eliminated the development of end-stage renal failure. Furthermore, the recently crossed-over patients did benefit from the later initiation of the ACE inhibitor.[132]

A study comparing captopril and nifedipine prospectively[133] for 3 years reported that there was no difference in outcome between groups. This study confirmed the findings from a smaller trial that reported a slower rate of decline of function in both groups, but more patients with "renal death" in the nifedipine than in the captopril group.[134]

XV Reversible and nonreversible airway disease

Recommendations

1. In patients with reversible airway disease, β-adrenergic antagonists should be avoided (grade A).
2. In patients taking β_2-adrenoceptor agonists as bronchodilators, if diuretic treatment is prescribed, a combination of a potassium-sparing diuretic and a thiazide is preferred (grade B).

Background

Since bronchodilator therapy with β_2-adrenoceptor agonists may decrease serum potassium, diuretic-induced hypokalemia should be avoided to minimize the risk of hypokalemia-induced arrhythmias. Regarding the bronchial effects of antihypertensive drugs, both cardioselective and noncardioselective β_2-adrenergic antagonists can cause bronchospasm, even after topical ophthalmologic application.[135] α-adrenergic antagonists and calcium-channel blockers may have a small bronchodilator effect.[136,137] Notably, ACE inhibitors can cause a dry cough and also the development of nonspecific airway hyperreactivity.[138,139] Thus, not only cough but also asthmatic symptoms should be considered as possible adverse reactions to ACE inhibitors.

XVI Hyperuricemia and gout

Recommendations

1. Asymptomatic hyperuricemia (i.e., in the absence of gout) does not require treatment per se and is not a contraindication for diuretic therapy (grade D).
2. Obese men and women with a high alcohol intake are the most prone to develop gout on a thiazide diuretic. In these patients, diuretic therapy should be avoided (grade D).
3. In patients with a history of gout, diuretics should be avoided. If a diuretic is essential for the control of hypertension in a patient with a history of gout, gout can be prevented by the concurrent use of allopurinol (grade D).

Background

The risk of having an attack of gout appears to be dependent on the degree of increase in serum uric acid irrespective of its cause. With low-dose diuretics, attacks of gout occur rarely. However, if they do occur, this is an indication to lower the dose further or to discontinue the diuretic altogether.[140] At present, there is insufficient evidence to conclude that hyperuricemia per se is an independent risk factor for cardiovascular disease.[141] It is more likely that uric acid is a marker for other risk factors.[141–145]

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supported research and have received consultancy fees from various pharmaceutical companies; Dr. Spence has also applied for a patent for DMSA for treatment of homocysteiemia in dialysis patients. Dr. Campbell has received consultancy fees and speaker's fees from various pharmaceutical companies. Drs. Carruthers and Larochelle have conducted industry-supported research and have received consultancy fees and speakers' fees from various pharmaceutical companies. Dr. Feldman has conducted industry-supported research; he is a member of advisory boards for, and has received speaker's fees from, various pharmaceutical companies. Dr. Leenen has conducted industry-supported research and is a member of advisory boards for various pharmaceutical companies. Dr. Myers has conducted industry-supported research; he is member of advisory boards for, and has received speaker's fees from, various pharmaceutical companies. Dr. Zarnke has conducted industry-supported research.

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Considerations in the use of antihypertensive drug classes

Class of medications	When to use	When not to use
β-adrenergic antagonists	Post-MI, angina, uncomplicated hypertension (preferred therapy), diabetes (without nephropathy)	Asthma, peripheral vascular disease (severe)
α-adrenergic antagonists/ central acting agents	Uncomplicated hypertension (alternative therapy)	Autonomic dysfunction
ACE inhibitors	Diabetes, post-MI, heart failure, renal disease, uncomplicated hypertension (preferred therapy)	Bilateral renovascular disease, pregnancy
Angiotensin II antagonists	Diabetes (alternative therapy), heart failure (alternative therapy), uncomplicated hypertension (alternative therapy)	Bilateral renovascular disease, pregnancy
Diuretics		
Loop diuretics	Renal insufficiency (additional therapy)	Gout
Potassium-sparing agents	Additional therapy in combination with thiazide diuretics, primary hyperaldosteronism	Renal insufficiency
Thiazides	Uncomplicated hypertension (preferred therapy), systolic hypertension in the elderly (preferred therapy, suitable for older diabetic patients without nephropathy)	Gout, dyslipidemia (high dose)
Calcium-channel blockers		
Nondihydropyridines	Uncomplicated hypertension (alternative therapy)	Heart block, heart failure
Dihydropyridines	Systolic hypertension (preferred therapy) uncomplicated hypertension (alternative therapy)	

MI = myocardial infarction.

Considerations in the individualization of antihypertensive therapy

Risk factor/disease	Preferred therapy	Alternative therapy	Avoid therapy
Dyslipidemia	Thiazide diuretics (low dose), ß-adrenergic antagonists (with ISA), ACE inhibitors	α-adrenergic antagonists, angiotensin II antagonists, calcium-channel blockers, central acting agents	ß-adrenergic antagonists (non-ISA)
Diabetes mellitus	*With nephropathy:* ACE inhibitors *Without nephropathy:* ACE inhibitors or ß-adrenergic antagonists *With systolic hypertension:* low-dose thiazide or longer acting dihydropyridine calcium-channel blockers	Angiotensin II antagonists	High-dose diuretics, α-adrenergic antagonists and centrally acting agents (in the setting of autonomic neuropathy)
Smoking	Thiazide diuretics, ACE inhibitors		ß-adrenergic antagonists
Systolic hypertension older than 60 years	Thiazide diuretics, calcium-channel blockers	Angiotensin II antagonists, ACE inhibitors	α-adrenergic antagonists, centrally acting agents
Angina/prior myocardial infarction	ß-adrenergic antagonists, ACE inhibitors	Calcium-channel blockers (diltiazem, verapamil)	
Systolic dysfunction	ACE inhibitors (thiazide diuretics as additive therapy)	Angiotensin II antagonists, hydralazine/isosorbide dinitrate	
Peripheral arterial disease	As for uncomplicated hypertension	As for uncomplicated hypertension	ß-adrenergic antagonists (with severe disease)
Renal disease	ACE inhibitors (thiazide diuretics as additive therapy)	Dihydropyridine calcium-channel blockers	

ISA = intrinsic sympathomimetic activity.

Clinical problem solving based on the 1999 Canadian recommendations for the management of hypertension

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The diagnosis and treatment of hypertension remains a significant challenge in Canada, despite the widespread accessibility of resources for the detection of hypertension and the availability of very effective therapy. The recent Canadian Heart Health Survey reported that hypertension remains a common disease, with a prevalence of 22% among adults of 18 to 70 years of age.[1] Of these 4.1 million Canadians, only 16% have their hypertension treated and controlled.[1]

The cause of the gap between the rates of blood pressure control under optimal conditions (i.e., those achieved in clinical trials) and the current rates of blood pressure control achieved in the community is multifactorial; public health factors may have an impact on the low rates of awareness that patients have of their diagnosis of hypertension,[1] and behavioural factors may affect both the low levels of patient adherence to antihypertensive treatments and the relative insensitivity of health care providers in responding to inadequate degrees of blood pressure control.[2] In response to the perception that one factor contributing to this gap was the incomplete penetration among health care professionals of recommendations for the optimal diagnosis and treatment of hypertension, a revision of those recommendations was initiated. In addition, it was appreciated that the results of recent clinical trials that were not available when the recommendations were last revised have altered our approaches to the management of hypertension The generation of the 1999 recommendations, based on a critical review of the evidence, is intended to be the initial step in a multistep process to improve blood pressure control rates. This process includes the development of the recommendations that are outlined in the appended supplement, as well as the development of clinical practice guidelines that consider the following: (1) the therapies that can be proved to be most effective for an individual and (2) the cost-benefit relationship of these therapies. This process also includes the development of strategies to implement the clinical practice guidelines.

The *1999 Canadian Recommendations for the Management of Hypertension* do not contain any revolutionary changes compared with the 1993 version.[3] However, several evolutionary trends should be noted. Among the diagnostic recommendations, the utility of non-office-based measures of blood pressure (home blood pressure monitoring and automatic ambulatory blood pressure monitoring) was more strongly supported both in the assessment of prognosis as well as in the monitoring of therapy (see Diagnosis, Sections IV and V, page S5). In contrast, the role of echocardiography has remained restricted (see Diagnosis, Section VI, page S6). Among the pharmacological recommendations, the target blood pressures have been substantially lowered for those patients with diabetes and with renal disease (to less than 130/80 mm Hg and to less than 125/75 in patients with proteinuria of greater than 1 g/day). Notably, in the treatment of uncomplicated hypertension, ACE inhibitors have been added to thiazide diuretics and β-adrenergic antagonists as first-line recommendations (see Pharmacological Treatment, Section II, page S7). In the treatment of older patients with systolic hypertension, both thiazide diuretics and longer-acting dihydropyridine calcium-channel blockers have been recommended as first-line therapies (see Pharmacological Treatment, Section III, page S8). However, the major theme underlying the pharmacological recommendations is that, for any individual patient, the specific choice of an antihypertensive is much more dependent on the existence of concomitant risk factors or concurrent diseases, or both, than the extent of blood pressure elevation.

What initial conclusions can practitioners reach regarding the impact of these

recommendations on the management of their hypertensive patients? In the illustrative cases described below, we have tried to link these recommendations to practice.

Case 1

Marie is a 29-year-old pharmaceutical company representative whom you have seen once a month to check her blood pressure. Over the past 12 months, it has varied from 140/92 to 155/97 mm Hg. Eight years ago, she had gestational hypertension with her first pregnancy that resolved post partum. Over the past 4 months, her weight has increased by 3 kg. She does attempt to exercise at least 3 times weekly and tries to restrict the salt in her diet. She has less than one standard drink of alcohol daily. There is a family history of hypertension. On your examination, her blood pressure is 145/96 mm Hg. The findings of the rest of the physical examination, including funduscopic examination, are perfectly normal.

Is she hypertensive? Should she be treated?

The diagnosis of hypertension is still primarily made in the office. A blood pressure elevation of greater than 140/90 on at least 5 occasions over a 6-month period is a recommended criterion of diagnosis of elevated blood pressure (see Diagnosis, Section II, page S4). However, it is important to note 2 significant caveats to determining diagnosis and prognosis (and, hence, management decisions) based solely on office determinations of blood pressure. First, recommended techniques for blood pressure measurement by sphygmomanometer are rarely followed in general practice.[4,5] This can lead to a significant discrepancy in blood pressure measurement (as compared with gold-standard approaches). These inaccuracies can significantly affect the ability of practitioners to determine a diagnosis of hypertension. Second, it has been appreciated that non-office-based measures of blood pressure monitoring (home blood pressure monitoring and automatic ambulatory blood pressure monitoring) play an important role in the determination of the prognosis of a patient who is classified as hypertensive based on office determinations (see Diagnosis, Sections IV and V, page S5–S6). This is especially notable with regard to a diagnosis of office-induced hypertension (a disease that carries a much more benign prognosis than sustained hypertension). For the diagnosis of office-induced hypertension (versus sustained hypertension), either home blood pressure monitoring or automatic ambulatory blood pressure monitoring is required.

You send Marie home with a blood pressure monitor. (You have a dozen that you rent out for short-term use to your patients.) She reports back that the blood pressures she determines at home are similar to those that you have measured in the office. On her next visit, you review the laboratory studies taken in conjunction with her last visit. There are no abnormalities on urinalysis or complete blood count. Her serum potassium was 4.5 mmol/L. Serum creatinine was less than 100 mmol/L. Her fasting glucose was 5.2 mmol/L. Total cholesterol was 4.85 mmol/L with high-density lipoprotein (HDL) cholesterol of 1.32 mmol/L, low-density lipoprotein (LDL) cholesterol of 3.1 mmol/L and triglycerides of 2.2 mmol/L. Her ECG did not reveal any evidence of left ventricular hypertrophy.

Is she at increased risk of atherosclerotic complications due to her hypertension? Failing effective lifestyle modifications to lower her blood pressure, should she be treated pharmacologically?

Marie's risk of hypertension-related complications primarily reflects her risk of atherosclerotic complications, which would be mainly coronary artery disease and stroke. If she fails to lower her blood pressure, having made a genuine attempt at lifestyle modification (i.e., weight loss and increased exercise), the decision for instituting pharmacological therapy should be made based on considerations of the potential benefits of therapy versus risk. What are the potential benefits? Based on tables of risk ratios derived from the Framingham population base,[6] one can estimate that Marie's 10-year risk of coronary atherosclerotic complications, reflecting both her level of blood pressure as well as her other risk factors, is less than 1%. Furthermore, based on clinical trial experience, the potential benefit of antihypertensive therapy in reducing cardiovascular event rates (specifically, coronary artery disease complications) is only approximately 15%.[7] Thus, one would need to treat almost 700 patients like Marie in order to save one coronary event over the next 10 years. This "number needed to treat" of 700 does not compare favourably with those associated with other prophylactic treatment strategies (e.g., over the same period one would only need to prescribe Coumadin to fewer than 10 patients with atrial fibrillation to avoid a stroke). In summary, on a population basis, treatment of patients whose blood pressure is greater than 140/90 mm Hg in order to achieve a target blood pressure of less than 140/90 mm Hg does more good than harm (see Pharmacological Treatment, Section I, page S6). However, the decision to initiate drug therapy needs to include consideration not only of the level of blood pressure but also of the presence (or absence) of other concomitant risk factors and diseases. Thus, the approach you may take with Marie contrasts significantly with that taken with the patient with identical blood pressure who has diabetic nephropathy. In that patient, drug therapy should be considered for blood pressures greater than 130/80 mm Hg, with the aim of lowering the blood pressure to less than 130/80 mm Hg (see Pharmacological Treatment, Section VII, page S9).

Case 2

Doug is a 47-year-old middle manager with long-standing hypertension. He smokes a pack and a half of cigarettes a day and has symptoms consistent with a mild degree of chronic bronchitis, although he denies wheezing. His weight has been increasing steadily over the last 10 years, and he has a current

body mass index of 27.4 kg/m2. His blood pressure has been well controlled in the past with a β-adrenergic antagonist that was discontinued for reasons that are unclear. Currently, his blood pressures are in the range of 140/92 to 150/98 mm Hg. You have just taken him on as a new patient (his previous family physician relocated to an underserviced area in Toronto). On laboratory evaluation, his total cholesterol was 6.25 mmol/L with an HDL cholesterol of 0.97 mmol/L. Fasting serum glucose was 5.9 mmol/L.

Should Doug be treated pharmacologically? With what?

In contrast to Marie, Doug presents with a significantly higher risk of cardiovascular complications. His 10-year risk of coronary heart disease complications approaches 20%. Adequate blood pressure control would be expected to reduce his risk at least 3%. This translates into a number needed to treat of 33.

Approach to therapy (i.e., reducing his overall cardiovascular risk) needs to start with attempts at lifestyle modification.[8] It would be expected that giving up smoking would result in a much more significant reduction in cardiovascular risk (about 7%, number needed to treat 14) and should be encouraged. Weight reduction would be important, both for blood pressure control and for treatment of his hypercholesterolemia. As noted above, lifestyle modification therapy should be considered both as initial therapy and as an adjunct to pharmacological management.[6]

The choice of antihypertensive therapy reflects the nature of his hypertension (diastolic elevations in a patient under 60 years of age), his concomitant cardiovascular risk factors (i.e., smoking and hypercholesterolemia), as well as his obesity. The recommendations for first-line therapy for patients with uncomplicated hypertension include β-adrenergic antagonists diuretics and angiotensin-converting-enzyme (ACE) inhibitors. However, the choice of therapy for Doug reflects further considerations that underscore the importance of individualizing therapy based on other cardiovascular risk factors and concomitant diseases. His previous therapy with β-adrenergic antagonists may not be preferred therapy based on several considerations:

1. The benefits of β-adrenergic antagonist therapy in hypertensive smokers remain uncertain, thus, they are not recommended for hypertensives who smoke, in the absence of target-organ damage or concurrent cardiovascular disease (see Pharmacological Treatment, Section VI, page S9).
2. β-Adrenergic antagonists may impair the ability of the patient to benefit from exercise and may impede the ability of obese hypertensive patients to lose weight.[9] Although β-adrenergic antagonists are not contraindicated in hypertensive patients with hyperlipidemia, those without intrinsic sympathomimetic activity may develop a worse lipid profile (see Pharmacological Treatment, Section V, page S8).

Based on those considerations, therapy should be initiated to lower the patient's blood pressure to less than 140/90 mm Hg. First-line therapy should either be with a low-dose thiazide diuretic (since at lower doses the effects of thiazides on lipid profiles are minimal) or an ACE inhibitor. If there is a partial response to either agent, the other should be added in combination.

Case 3

Roy is a 67-year-old retired bureaucrat who facilitates consensus conferences in his leisure time. Several months ago, in conjunction with his yearly rectal examination, you noted that his blood pressure was 176/85 mm Hg. Repeated blood pressure measurements over the next 6 months demonstrated a consistent level of systolic hypertension. There were no other abnormalities in the rest of his physical examination. On laboratory studies, his total cholesterol was marginally elevated at 5.7 mmol/L, as was his fasting serum glucose at 8.3 mmol/L. You were able to convince him to reduce his alcohol intake, lose 4 kg and exercise more. Notwithstanding, his systolic blood pressures remained consistently greater than 160 mm Hg. Serum glucose, although decreased, was still elevated at 7.3 mmol/L. There were no other abnormalities on serum electrolytes, creatinine or urinalysis.

Should you treat his hypertension pharmacologically? With what?

In patients over the age of 60 years, systolic elevations of blood pressure greater than 160 mm Hg should be treated, even in the absence of other risk factors (see Pharmacological Treatment, Section III, page S8). Major considerations affecting your choice of therapy would include consideration of the recommendations for first line-therapy in the treatment of systolic hypertension, as well as the recommendations for the treatment of the hypertensive patient with diabetes. For older patients with systolic hypertension, preferred therapy is either a low-dose thiazide diuretic or a long-acting dihydropyridine calcium channel antagonist. Both of these classes of drugs have been shown to reduce both blood pressure and cardiovascular complications in older patients with systolic hypertension. Furthermore, in the absence of diabetic nephropathy, low-dose thiazides or long-acting dihydropyridine calcium channel antagonists remain the drug of choice for patients with systolic hypertension and Type II diabetes mellitus. However, your target for blood pressure control should be lower for those patients with diabetes than for those without (based on the findings of the HOT[10] and UKPDS 38[11] studies). As noted above, in the revised recommendations a target of less than 130/80 mm Hg is recommended for patients with hypertension and diabetes.

How would the development of proteinuria affect your choice for Roy?

For patients with diabetes, hypertension and overt nephropathy (defined as albuminuria greater than 300 mg/day), preferred therapy is an ACE inhibitor (see Pharmacological Treatment, Section VII, page S9).

To achieve target blood pressures, the increasing use of combination therapies should be considered. The 1999 recommendations note that a long-acting calcium-channel blocker may be combined with an ACE inhibitor or a low-dose thiazide diuretic may be added to an ACE inhibitor without adversely affecting microalbuminuria. Furthermore, for patients with adverse reactions to an ACE inhibitor, an angiotensin II receptor antagonist may be substituted.

Summary

The *1999 Canadian Recommendations for the Management of Hypertension* are notable for the trends that they represent with regard to the evolution of the management of hypertension. Diagnostically, the Recommendations endorse the greater use of non-office-based measures of blood pressure control and greater emphasis on the assessment of other atherosclerotic risk factors, both when considering prognosis in hypertension and in the choice of therapy.

On the treatment side of the equation, lower targets for blood pressure control have been advocated in subgroups of hypertensive patients, particularly in those with diabetes and renal disease. In conjunction with the recently published recommendations on lifestyle management, there is a greater emphasis on lifestyle modification, both as initial and adjunctive therapy in hypertension. Implicit in the recommendations for therapy is the principle that for the vast majority of hypertensive patients treated pharmacologically, practitioners should not follow a stepped-care approach. Instead, therapy should be individualized, primarily based on consideration of concurrent diseases, both cardiovascular and noncardiovascular (Tables 1 and 2). Through the consensus process, there was a general appreciation of how far we have come in the development of evidence-based recommendations for hypertension management. However, there was also an increasing appreciation of how far we have to go in effectively translating these recommendations into better blood pressure control.

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Table 1: Considerations in the use of antihypertensive drug classes

Class of medications	When to use	When not to use
β-adrenergic antagonists	Post-MI, angina, uncomplicated hypertension (preferred therapy), diabetes (without nephropathy)	Asthma, peripheral vascular disease (severe)
α-adrenergic antagonists/ central acting agents	Uncomplicated hypertension (alternative therapy)	Autonomic dysfunction
ACE inhibitors	Diabetes, post-MI, heart failure, renal disease, uncomplicated hypertension (preferred therapy)	Bilateral renovascular disease, pregnancy
Angiotensin II antagonists	Diabetes (alternative therapy), heart failure (alternative therapy), uncomplicated hypertension (alternative therapy)	Bilateral renovascular disease, pregnancy
Diuretics		
Loop diuretics	Renal insufficiency (additional therapy)	Gout
Potassium-sparing agents	Additional therapy in combination with thiazide diuretics, primary hyperaldosteronism	Renal insufficiency
Thiazides	Uncomplicated hypertension (preferred therapy), systolic hypertension in the elderly (preferred therapy, suitable for older diabetic patients without nephropathy)	Gout, dyslipidemia (high dose)
Calcium-channel blockers		
Nondihydropyridines	Uncomplicated hypertension (alternative therapy)	Heart block, heart failure
Dihydropyridines	Systolic hypertension (preferred therapy) uncomplicated hypertension (alternative therapy)	

MI = myocardial infarction.

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Table 2: Considerations in the individualization of antihypertensive therapy

Risk factor/disease	Preferred therapy	Alternative therapy	Avoid therapy
Dyslipidemia	Thiazide diuretics (low dose), ß-adrenergic antagonists (with ISA), ACE inhibitors	α-adrenergic antagonists, angiotensin II antagonists, calcium-channel blockers, central acting agents	ß-adrenergic antagonists (non-ISA)
Diabetes mellitus	*With nephropathy:* ACE inhibitors *Without nephropathy:* ACE inhibitors or ß-adrenergic antagonists *With systolic hypertension:* low-dose thiazide or longer acting dihydropyridine calcium-channel blockers	Angiotensin II antagonists	High-dose diuretics, α-adrenergic antagonists and centrally acting agents (in the setting of autonomic neuropathy)
Smoking	Thiazide diuretics, ACE inhibitors		ß-adrenergic antagonists
Systolic hypertension older than 60 years	Thiazide diuretics, calcium-channel blockers	Angiotensin II antagonists, ACE inhibitors	α-adrenergic antagonists, centrally acting agents
Angina/prior myocardial infarction	ß-adrenergic antagonists, ACE inhibitors	Calcium-channel blockers (diltiazem, verapamil)	
Systolic dysfunction	ACE inhibitors (thiazide diuretics as additive therapy)	Angiotensin II antagonists, hydralazine/isosorbide dinitrate	
Peripheral arterial disease	As for uncomplicated hypertension	As for uncomplicated hypertension	ß-adrenergic antagonists (with severe disease)
Renal disease	ACE inhibitors (thiazide diuretics as additive therapy)	Dihydropyridine calcium-channel blockers	

ISA = intrinsic sympathomimetic activity.