

May 2003

**The Canadian Hypertension Education Program Recommendations:
what's new, what's old but still important in 2003.**

The Bottom Line Version

On behalf of the Evidence Based Recommendations Task Force of the Canadian Hypertension
Education Program

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Introduction

This summary outlines the ongoing efforts of the majority of hypertension specialists in Canada to develop and update evidence-based recommendations for the management of hypertension. This effort, initiated on a yearly basis in 1999, represents much more than an academic exercise. It has clearly been recognized that our ability to influence health care professionals and improve the management of hypertension starts with the dissemination of up-to-date, credible, management recommendations. In this respect, the Evidence-based Recommendations Task Force has been increasingly coupled to a very active dissemination and implementation program (and more recently an evaluation program to monitor the impact of our efforts). This coordinated network of i) the Evidence-based Recommendations Task Force, ii) the Implementation Task Force and iii) the Evaluation Task Force comprise the Canadian Hypertension Education Program (CHEP). This initiative is supported by a coalition of health care professional societies with a stake in the management of hypertension, including The Canadian Hypertension Society, The Canadian Coalition for High Blood Pressure Prevention and Control, The College of Family Physicians of Canada, Health Canada, and The Heart and Stroke Foundation of Canada.

Hypertension remains a major public health problem in Canada. Hypertension is common (as a reason to visit a physician in Canada) (1) and is a significant cause of morbidity and mortality. In countries like Canada, hypertension is the leading risk associated with death in women and the second leading risk in men (2). Further, hypertension is only marginally treated (there is no indication that blood pressure control rates have risen appreciably over the past 10 years since the Canadian Heart Health Survey) (3). However, there have been recent indications that the patterns of management of hypertension in Canada are improving (or at least that patterns of management have been positively influenced) following adoption of our yearly process of updating the hypertension recommendations (NR Campbell et. al., *Journal of Hypertension*, in press). Thus, the existing version of the CHEP recommendations for the management of hypertension should be seen as the 2003 blueprint for the ongoing development of tools and programs to improve hypertension management, blood pressure control, and ultimately reduce blood pressure-related complications in Canada.

This year's recommendations process (i.e., the evaluation of hypertension-related trials in 2002 and their incorporation into revised recommendations) was in some respects both very typical and highly atypical (Table 1). Typically, the subgroups prepared draft recommendations in the spring and summer of 2002 that were discussed at our yearly consensus conference in Edmonton in October 2002 and subsequently ratified according to our previously established process (4). Atypically, the process was re-opened and extended into 2003 based on the impact of a single trial that was published following completion of our yearly process (but prior to release of our recommendations). The publication of ALLHAT (5), the single largest hypertension trial ever conducted, necessitated a re-appraisal of those recommendations potentially impacted by the results of the study. All subcommittees were asked to examine the study based on a position paper circulated from the Central Review Committee of the *Task Force*. Recommendations related to i) patients with hypertension and diabetes, and ii) patients with hypertension and no other compelling indications (i.e., the subgroup previously classified as uncomplicated hypertension) were revised and subsequently endorsed by a consensus of the members of the

Task Force. Thus, the present recommendations incorporate at least an initial review of ALLHAT, as well as some consideration of ANBP-2 (6) (another major study that was published just as the revised recommendations were being reformulated).

The current summary is designed as a rapid publication to highlight the results of these considerations, and specifically, to identify those aspects of the recommendations that are new or existing but still important.

What's New for the 2003 Recommendations?

The major focus of the 2003 update was the incorporation of the findings of the major treatment studies from 2001-2002 into the recommendations. The most important of these studies were PROGRESS, IDNT, RENAAL (these papers were published in 2001 but were the focus of ongoing discussion in 2002), LIFE and ALLHAT. These studies influenced the recommendations in regards to therapeutic considerations for a) patients with hypertension and diabetes, b) patients with hypertension and other concurrent cardiovascular diseases, and c) patients with hypertension without other compelling indications (previously known as uncomplicated hypertension).

The ALLHAT study, published following completion of the Recommendations process, undoubtedly had the biggest impact on this year's **process**, although ultimately, the conclusions from ALLHAT resulted in only subtle changes to the actual recommendations. This landmark study, examined the effect of amlodipine- or lisinopril- vs. chlorthalidone-based treatment regimens (an alpha blocker arm was prematurely discontinued in 2000 due to excess stroke and heart failure) in 33,357 participants older than 55 years with hypertension and at least one other CHD risk factor. The primary endpoint was fatal CHD or non-fatal MI. Mean age of the study population was 67 years, 35% were black, and 36% had diabetes. Baseline blood pressure was 146/84 mm Hg (however, pre-existing medications were continued to the point of randomization). Overall, blood pressure control was approximately 20% better in the chlorthalidone group than with lisinopril, and approximately 10% better than with amlodipine, and neither the primary outcome measures nor all-cause mortality differed between the groups. However, the incidence of heart failure was significantly higher (38%) with amlodipine vs. chlorthalidone. In the comparison of lisinopril and chlorthalidone, there was a 10% higher rate of combined CHD, 15% higher stroke rate, and 19% higher heart failure rate with lisinopril. Notwithstanding differences in blood pressure control between treatment arms and concerns over whether the heart failure diagnoses were adequately validated (which may have accounted for some of the differences seen in the secondary endpoint analyses), it was concluded by the *Evidence-based Recommendations Task Force* that ALLHAT did demonstrate at least comparable effectiveness of a diuretic-based regimen in both reducing blood pressure and reducing hypertension-related cardiovascular complications. In that respect, the ALLHAT study was recognized to confirm the tenet, that in the pharmacological treatment of hypertension in "undifferentiated patients", thiazide diuretics remain the "first among equals". Further, subgroup analysis confirmed the relative effectiveness of a diuretic-based regimen in patients with hypertension and diabetes (demonstrated previously in the SHEP study) (7). Notably, the poorer outcomes with lisinopril in both reducing blood pressure and reducing hypertension-related cardiovascular complications were most evident in the black subgroup.

The ALLHAT study was also seen as important in underscoring the message that pharmacological therapy of hypertension “means” combination drug therapy for the majority of hypertensives (63% of the patients in ALLHAT required two or more drugs and only 70% achieved blood pressure control).

Based on ALLHAT, is it fair to conclude that diuretics should be recommended as sole “first-line” therapy in the management of hypertension in patients “without other compelling indications”? Considering the evidence to date, the answer would have to be no. A formal evaluation of the results of ANBP-2 was not part of the 2003 recommendations. However, it was appreciated that the results of this study (which demonstrated the superiority of an ACE-inhibitor-based regimen over a diuretic-based regimen in older patients with hypertension) underscored the fallacy of concluding that any one of the five recommended first-line agents demonstrated clear overall superiority (in regards to effectiveness in either blood pressure lowering or reducing hypertension-related cardiovascular risk). The validity of assuming the superiority of diuretics is further questioned by the lack of comparison with other first-line therapies in ALLHAT (i.e., beta blockers and angiotensin II receptor blockers). Finally, the long-term adverse impact of the increase in blood glucose demonstrated in the diuretic arm of ALLHAT is unknown but remains a concern mitigating against a blanket endorsement of thiazide diuretics as unambiguous preferred therapy in the initial pharmacological management of hypertension.

Overall, the implications of the ALLHAT study in regards to the 2003 Recommendations were reflected in:

- a) changes in wording related to choice of first line therapy, increasing the prominence of thiazide diuretics**
- b) a recommendation NOT to consider ACE-inhibitors as first line therapy in black hypertensives without other compelling indications (reflecting the decreased blood pressure lowering effectiveness of this class of drugs in this population)**
- c) a recommendation to consider diuretics as a safe alternative to ACE-inhibitors and angiotensin receptor blockers in patients with hypertension, and diabetes but NORMAL urinary albumin excretion**

The LIFE trial (8) also had a significant impact on the deliberations. This study compared the benefits of a beta-blocker-based regimen (with atenolol) vs. an angiotensin II receptor blocker (ARB) based regimen (with losartan) in hypertensive subjects older than 55 years with left ventricular hypertrophy. LIFE demonstrated a significant benefit of ARB-based therapy. It was felt that the LIFE study entry criteria resulted in the inclusion of a high risk hypertensive population that would be comparable to the highest risk subgroups included in prior large hypertension trials (i.e., subgroups which would have disproportionately contributed to the total endpoints of those previous studies). Thus, it was felt that the extrapolation of LIFE results to patients with “uncomplicated” hypertension was appropriate. However, concerns were raised that the control regimen (atenolol) has uncertain efficacy in older hypertensives. As such, any assertion that ARB-based therapy is superior to “proven first line therapy” could not be supported.

Overall, the implications of the LIFE study were reflected in:

- a) **the recommendation that ARBs be considered as an additional option for first-line therapy in younger patients, along with thiazide diuretics, beta-blockers, dihydropyridine calcium channel blockers and angiotensin converting enzyme inhibitors**
- b) **the recommendation of ARBs as a first line choice for the treatment of ISH, along with diuretics and dihydropyridine calcium channel blockers (based, in part, on review of the subgroup analysis of patients in the LIFE study with isolated systolic hypertension [ISH])**
- c) **the development of more specific recommendations regarding preferred first-line therapies for the treatment of hypertension in patients with left ventricular hypertrophy. These preferred therapies followed the recommendations for treatment of “hypertension in patients with no other compelling indications”.**

This year’s process also saw further simplification of the recommendations for the management of hypertension in patients with diabetes: **ACE-inhibitors or angiotensin receptor blockers were recommended as first line therapy in all subgroups of diabetic patients with hypertension.** This revision was based on considerations of the diabetic subgroup analysis of LIFE, as well as the ongoing discussions of the 2001 trials that established the renoprotective effect of angiotensin receptor blockers (i.e., RENAAL [9] and IDNT [10]).

What’s old but still important?

- 1) **Individualizing management of hypertension based on overall atherosclerotic risk.** It remains axiomatic (but somewhat paradoxical) that concurrence of other cardiovascular risk factors has a greater impact on both atherosclerotic risk and the absolute benefit of antihypertensive therapy than the extent of blood pressure elevation itself. Further, concurrence of other risk factors/cardiovascular disease continues to have implications both in terms of targets for treatment as well as specific therapeutic choices (Tables 3, 4). As demonstrated by the Framingham Heart Study Group (11), in the general population even blood pressures within a “normal” range are positively correlated with cardiovascular risk. Thus, patients with “high normal” blood pressures (130-139/85-89 mm Hg) have a three times greater risk of cardiovascular events than those with “optimal” blood pressures (SBP less than 120 mm Hg). Although these data cannot predicate drug management decisions in the general population, they are being seen as increasingly important in identifying blood pressure targets for treatment in patients at highest risk for atherosclerotic events. For example, treatment of hypertension is much more effective, in terms of absolute cardiovascular risk reduction, in patients with diabetes and “high-normal blood pressure” than in premenopausal females with no other risk factors and Level 2 Hypertension (greater than 160/100) (12,13). Whether lower blood pressure thresholds/targets for treatment can be justified for other subgroups at highest risk for atherosclerotic complications (e.g., patients post-stroke, or those patients who fulfill the entry criteria for the HOPE study) (14) is an ongoing focus of discussion for 2003.

- 2) **Lifestyle modifications remain a cornerstone of antihypertensive therapy.** Lifestyle modification is critical both as initial management and in conjunction with pharmacological therapy. (Table 5). Recent data indicates a lifetime risk for developing hypertension of over 90% (15). These findings emphasize the importance of lifestyle changes in the prevention as well as the management of hypertension.
- 3) **The role of combination therapy remains critical in hypertension control.** This message is important, both in the context of combining lifestyle and pharmacological treatment, as well as combining antihypertensive drugs effectively. The vast majority of hypertensive patients require combination drug therapy. The most effective combinations should be used preferentially (Table 6). Whether this predicts an expanded role for the use of fixed dose combinations in the management of hypertension will probably be dependent on their, as yet, unproven role in improving compliance and ultimately blood pressure control.
- 4) **Establishing and maintaining patient adherence, compliance, convergence or concordance** (pick your favorite term) with their antihypertensive management prescription remains a major issue (and a major focus of ongoing discussion and study). However, attention to some simple approaches can improve patient adherence (Table 7).

In some ways, more important than “what’s new” in the 2003 Recommendations is “what has stayed the same”. Hypertension remains a significant public health problem and many of the issues in the management of hypertension in 2002 remain in 2003. The tools to control hypertension and to reduce cardiovascular disease are in our hands. The Canadian Hypertension Education Program will continue to advocate for hypertension treatment and control, increase awareness of the importance of optimum hypertension management, develop tools to aid health care professions and evaluate the impact of our activities. We will continue to provide the most current evidence based recommendations to Canadian health care practitioners.

Table 1

**CHEP: The 2003 Recommendations for the Management of Hypertension:
How Were the New Recommendations Formulated?**

- Review of literature over preceding year by expert subcommittees, grading of literature and formulation of draft recommendations based on new trials (Apr-Aug 2002)
- Negotiation between subcommittees and Central Review Committee (Aug-Sept 2002)
- Presentation/discussion/revision (or rejection) of draft recommendations in plenary session of the members of the Evidence-based Recommendations Task Force (Oct 2002)
- Presentation of draft recommendations at an open forum (Oct 2002)
- Circulation of recommendations to task force members for voting (Nov 2002)
- Re-review of ratified recommendations following release of ALLHAT (Jan-Mar 2003)
- Revision of recommendations and ratification (Mar 2003)

Table 2

Key Aspects of the 2003 CHEP Recommendations for the Management of Hypertension

What's new?

- Broadening of recommendations for first-line therapy including angiotensin II receptor blockers
- Simplification of recommendations for the management of patients with diabetes and hypertension with the universal recommendation of either angiotensin receptor blockers and angiotensin converting enzyme inhibitors as preferred therapy

What's old but still important?

- Assessment of global atherosclerotic risk in hypertensive patients including the appreciation of lower blood pressure targets for patients at highest atherosclerotic risk
- Importance of lifestyle modifications as a cornerstone of anti-atherosclerotic therapy
- Emphasis of the benefits of thiazide diuretics in all subgroups of hypertensive patients
- Importance of drug combinations for blood pressure control
- Focus on adherence/concordance/compliance

Table 3

Target Values for Blood Pressure

<u>Condition</u>	<u>Target (SBP/DBP mmHg)</u>
Diastolic ± systolic hypertension	<140/90
Isolated systolic hypertension	<140
Home BP measurement (no diabetes)	<135/85
Renal disease or proteinuria)	
Diabetes	<130/80
Renal disease	<130/80
Proteinuria >1g/day	<125/75

Table 4 Considerations in the Individualization of Antihypertensive Therapy

*When using two drugs specifically to lower blood pressure, use Table 6 to maximize the hypotensive effect. Short acting calcium channel blockers are not recommended in the treatment of hypertension. ACE Angiotensin-converting enzyme; TIA transient ischemic attack; ARB angiotensin II receptor blocker

	<i>Initial Therapy</i>	<i>Second-line Therapy</i>	<i>Notes and/or Cautions</i>
Hypertension without other compelling indications	Thiazide diuretics, beta blockers, ACE-inhibitors, ARBs, or long-acting dihydropyridine calcium channel blockers	Combinations of first-line drugs (see Table 5)	Alpha-blockers are not recommended as initial therapy. Beta-blockers are not recommended in those over 60 years of age. Hypokalemia should be avoided by using potassium-sparing agents in those who are prescribed diuretics. ACE inhibitors are not recommended in blacks.
Isolated systolic hypertension without other compelling indications	Thiazide diuretics, ARBs or long-acting dihydropyridine calcium channel blockers	Combinations of first-line drugs	Hypokalemia should be avoided by using potassium-sparing agents 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 calcium channel blockers or an ARB/ACE inhibitor combination	
Diabetes mellitus without nephropathy	ACE inhibitors, ARBs or thiazide diuretics	Combination of first-line drugs or addition of cardioselective beta-blockers and/or long-acting calcium channel blockers	If the serum creatinine level is >150 μ mol/l, a loop diuretic should be used as a replacement for low-dose thiazide diuretics if volume control is required
Angina	Beta-blockers (consider adding ACE inhibitors)	Long-acting calcium channel blockers	Avoid short-acting nifedipine
Prior myocardial infarction	Beta-blockers and/or ACE inhibitors	Combinations of additional agents	
Heart Failure	ACE inhibitors (thiazide or loop diuretics, beta-blockers, spironolactone as additive therapy)	ARBs or hydralazine/isosorbide dinitrate	Avoid nondihydropyridine calcium channel blockers (diltiazem, verapamil)
Past cerebrovascular accident or TIA	ACE inhibitor/diuretic combinations		Blood pressure reduction reduces recurrent cerebrovascular events
Renal disease	ACE inhibitors (diuretics as additive therapy)	Combinations of additional agents	Avoid ACE inhibitors if bilateral renal artery stenosis
Left ventricular hypertrophy	ACE inhibitors, ARBs, dihydropyridine calcium channel blockers, diuretics, (beta-blockers for patients under 55 years)		Avoid hydralazine and minoxidil
Peripheral arterial disease	Does not affect initial treatment recommendations	Does not affect initial treatment recommendations	Avoid beta-blockers with severe disease
Dyslipidemia	Does not affect initial treatment recommendations	Does not affect initial treatment recommendations	

Table 5
Impact of Lifestyle Therapies on BP in Hypertensive Adults

<i>Intervention</i>	<i>Targeted change</i>	<i>SBP/DBP</i>
Sodium reduction	100 mmol/day	-5.8 / -2.5
Weight loss	-4.5 kg	-7.2 / -5.9
Alcohol reduction	-2.7 drinks/day	-4.6 / -2.3
Exercise	3 times/week	-10.3 / -7.5
Dietary patterns	DASH diet	-11.4 / -5.5

Table 6
Useful Antihypertensive Drug Combinations

For additive hypotensive effect in dual therapy, combine an agent from Column 1 with any in Column 2.

<i>Column 1</i>	<i>Column 2</i>
* Thiazide diuretic	* Beta-blocker
* Long-acting dihydropyridine calcium channel blocker	* ACE Inhibitor
	* ARB

Table 7
Recommendations to Improve Adherence to Antihypertensive Prescriptions

Adherence can be improved by a multi-pronged approach:

- Simplify medication regimens to once daily dosing
- Tailor pill-taking to fit patients' daily habits
- Encourage greater patient responsibility/autonomy in their BP management (including home BP monitoring)
- Educate patients and patients' families about their disease/treatment regimens

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