

# Clinical Focus:

New Issues in the Management of Hypertension

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## Getting to the Bottom of Hypertension

**H**ypertension is increasingly prevalent in Canada and around the world. Within an aging society such as ours, hypertension plays a leading role in the development of cardiovascular disease. A recent population-based survey estimated the prevalence of hypertension to be 21.1% among Canadians aged 18 to 74 years. In the U.S., approximately 25% of American adults (50 million) have hypertension. The prevalence of hypertension is higher in older persons, with at least 50% of Canadians over the age of 65 having this condition.

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PERSPECTIVE

Hypertension is a risk factor for myocardial infarction, congestive heart failure, stroke, renal failure and dementia. Elderly women and black patients are at particularly high risk of complications related to hypertension. In recent years, it has been recognized that systolic blood pressure is a stronger predictor of cardiovascular disease risk than is diastolic pressure. Isolated systolic hypertension, commonly diagnosed in older patients, is a particularly hazardous condition. The relationship between blood pressure and cardiovascular disease risk is continuous, and is dependent upon the severity and duration of hypertension, and is modified by the presence or absence of co-existing cardiovascular disease risk factors. The majority of hypertensive adults have at least one co-existing cardiovascular risk factor. Appropriate treatment of hypertension lowers the risk of cardiovascular mortality and morbidity, including the risk of myocardial infarction, stroke and heart failure.

Despite significant advances in the understanding, diagnosis and treatment of hypertension, there remains a large care gap in Canada in the management of hypertension. A recent study by Joffres demonstrated that 43% of Canadians with hypertension were unaware of their condition and were thus untreated. Of the remaining 57% of people with hypertension, 22% were untreated, 21% treated but uncontrolled, and only 13% were treated and controlled. The National Health and Nutrition Examination Surveys (NHANES) have shown that awareness of hypertension has improved in the U.S. over the past 25 years, as has the proportion of people with controlled hypertension, from 10% to over 27% (see Table 1). However, despite increasing awareness and treatment options, the majority of North Americans with hypertension still remain uncontrolled. Similar observations exist in many Western European countries.

Multiple, randomized, controlled, clinical trials have proven that treatment of hypertension reduces the risk of cardiovascular events. Over the past three decades, multiple new classes of effective antihypertensive agents have become available and have been shown to have comparable efficacy in lowering blood pressure. Significant reductions in morbidity and mortality attributable to hypertension have been noted during the same period. Age-adjusted death rates from stroke have declined by 60%, and coronary heart disease deaths have fallen by 53%. However, the rate of reduction in cardiovascular

mortality and morbidity has slowed since the early 1990s, and since then, the prevalence of congestive heart failure and the incidence of end-stage renal disease have increased substantially. Table 1 also demonstrates a relative slowing between 1988 and 1994 in the growth of awareness, treatment and control of hypertension. It has also been noted that there are socioeconomic, regional and ethnic variations in the prevalence of hypertension. Thus, considerable gains remain to be realized at a population level through more effective detection and management of hypertension.

DIAGNOSIS

Hypertension is defined as systolic blood pressure (SBP) of 140 mmHg or greater, diastolic blood pressure (DBP) of 90 mmHg or greater, or the need for antihypertensive medication. The *Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-VI)*, has proposed a classification of blood pressure that has been widely adopted in many countries, including Canada (see Table 2). Although the relationship between blood pressure and risk is continuous, arbitrary cut-offs between normal and abnormal blood pressure allow clinicians to focus on those at highest risk. A new category of “high normal blood pressure” has been added to reflect the continuous relationship between blood pressure and cardiovascular risk. It is imperative to diagnose hypertension appropriately, since such a diagnosis usually involves long-term therapy. Thus, accurate measurement technique and verification of elevated blood pressure on multiple occasions over time are important.

Blood pressure should be measured with the patient seated in a chair with his or her back supported, arm supported at heart level, and following five minutes of rest. Smoking and ingestion of caffeine should not have occurred within 30 minutes prior to having blood pressure measured. An appropriate-sized cuff should be used, with the bladder encircling at least 80% of the arm. A large cuff should be available when needed. A mercury sphygmomanometer is recommended for measurement, although a validated electronic device may be used. The first appearance of sound should be recorded as SBP, and the disappearance of sound as the DBP. At least two readings, separated by at least two minutes, should be recorded and averaged. In the absence of indications for immediate or urgent treatment of hypertension, blood pressure should be measured at several visits prior to establishing a

diagnosis of hypertension. Verification of elevated blood pressure in the contralateral arm should be made and recorded on at least one occasion.

Self-measurement of blood pressure may provide valuable information in establishing the diagnosis of hypertension and in determining the response to treatment. White-coat hypertension, in which clinic blood pressure is often higher than ambulatory blood pressure, may be present in up to 20% of patients with hypertension. White-coat hypertension is associated with a lower cardiovascular risk than is sustained hypertension; still, it may be

a precursor of sustained hypertension and requires ongoing surveillance. Validated electronic blood pressure measurement devices are appropriate for self-measurement, but they should be periodically compared to recordings taken with a mercury device. Finger monitors have significant potential for inaccuracy and should be avoided.

Ambulatory blood pressure measurement over a 24-hour period can also provide useful information in the treatment and risk-stratification of hypertensive subjects. Considerable evidence suggests that ambulatory blood pressure tends to be lower than

TABLE 1

Trends in the Awareness, Treatment and Control of High Blood Pressure in Adults: U.S. 1976–1994\*

	NHANES II (1976–80)	NHANES III Phase 1 (1988–91)	NHANES III Phase 2 (1991–94)
Awareness	51%	73%	68.4%
Treatment	31%	55%	53.6%
Control**	10%	29%	27.4%

\*Data are for adults aged 18 to 74 years with SBP ≥ 140 mmHg, DBP ≥ 90 mmHg, or taking antihypertensive medication.

\*\*SBP > 140 mmHg and DBP < 90 mmHg.

Adapted from: Burt V et al and unpublished NHANES III, phase 2 data provided by the Centers for Disease Control and Prevention, National Center for Health Statistics.

TABLE 2

Classification of Blood Pressure for Adults Aged 18 and Older\*

Category	Systolic (mmHg)	and/or	Diastolic (mmHg)
Optimal**	<120	and	<80
Normal	<130	and	<85
High-normal	130–139	or	85–89
Hypertension***			
Stage 1	140–159	or	90–99
Stage 2	160–179	or	100–109
Stage 3	≥ 180	or	≥ 110

\*Not taking antihypertensive drugs and not acutely ill. When systolic and diastolic blood pressures fell into different categories, the higher category should be selected to classify the individual's blood pressure status. For example, 160/92 mmHg should be classified as stage 2 hypertension, and 174/120 mmHg should be classified as stage 3 hypertension. Isolated systolic hypertension is defined as SBP of 140 mmHg or greater and DBP below 90 mmHg and staged appropriately (e.g. 170/82 mmHg is defined as stage 2 isolated systolic hypertension). In addition to classifying stages of hypertension on the basis of average blood pressure levels, clinicians should specify presence or absence of target organ disease and additional risk factors. This specificity is important for risk classification and treatment.

\*\* Optimal blood pressure with respect to cardiovascular risk is <120/80 mmHg. However, unusually low readings should be evaluated from clinical significance.

\*\*\* Based on the average of two or more readings taken at each of two or more visits after an initial screening.

Adapted from: National Institutes of Health: National Heart, Lung, and Blood Institute (National High Blood Pressure Education Program). *The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure*. NIH Publication No. 98-4080, November 1997.

clinic blood pressure and correlates better with markers of target organ damage such as left ventricular hypertrophy. Although evidence is lacking regarding the benefit of treatment decisions made on the basis of ambulatory blood pressure recordings alone, it does appear that patients with normal ambulatory measurements, despite elevated clinic blood pressure, may be a lower-risk group of patients with hypertension. Normal ambulatory blood pressure values are below 135/85 mmHg during waking hours and below 120/75 mmHg during sleep.

The evaluation of the patient with hypertension has three main objectives: to exclude secondary causes of hypertension; to determine the presence or absence of target organ damage or cardiovascular disease; and to diagnose and treat co-existing cardiovascular risk factors. Thus, hypertensive patients should undergo a thorough medical history and examination, which should include measurement of height, weight and waist circumference. Fundoscopic examination and evaluation of all palpable pulses are critical components

of an organized approach for the detection of target organ damage. In addition, certain investigations are routinely indicated in patients with hypertension. These include complete blood count, urinalysis, electrolytes, fasting glucose, urea, creatinine, 12-lead electrocardiogram, and a fasting lipid profile including triglycerides and low-density lipoprotein (LDL-C) and high-density lipoprotein (HDL-C). Essential hypertension is the diagnosis in over 90% of cases. In patients with severe or refractory hypertension, or with significant clinical or laboratory abnormalities, secondary causes such as renal disease, adrenal hypertension (Cushing's, pheochromocytoma) and renovascular hypertension should be excluded. Most of these conditions can be suspected by a careful history and physical examination (for example, renal bruit in renovascular hypertension, or intermittent hypertension with diaphoresis and headache in pheochromocytoma).

In some patients, additional tests may provide useful information, particularly for risk stratification but occasionally for decisions regarding treatment. These tests include uric

acid, urine microalbumin, creatinine clearance, serum calcium, thyroid-stimulating hormone (TSH) and glycosylated hemoglobin. In patients with a fourth heart sound (S4), or with electrocardiographic suspicion of left ventricular hypertrophy (LVH), echocardiography may be warranted to confirm the presence or absence of LVH, a powerful predictor of risk in hypertension.

The risk of cardiovascular disease in people with hypertension is further influenced by the presence or absence of target organ damage and concomitant risk factors or conditions. Thus, each patient with hypertension should undergo risk stratification during routine evaluation, which may then allow for appropriate timing and selection of antihypertensive therapy (see Table 3, page 5).

## TREATMENT

The primary objective of treating hypertension is to prevent cardiovascular disease and death. This is best achieved by lowering SBP to below 140 mmHg and DBP to below 90 mmHg,

and by parallel control of other modifiable risk factors. In certain patient populations, additional benefit may be realized by lowering blood pressure even lower, such as in patients with advanced renal disease, diabetes and congestive heart failure. The benefit of lowering blood pressure on reducing morbidity and mortality has been demonstrated in mild, moderate and severe hypertension, as well as in malignant hypertension. As risk rises with higher blood pressure and additional risk factors, a more aggressive treatment strategy is warranted, with a resultant greater absolute reduction in risk.

All patients with hypertension should initially be counselled regarding the importance of lifestyle modifications to lower blood pressure and prevent complications. This topic should be periodically revisited in future health encounters to promote compliance with lifestyle measures, which can be difficult to implement and maintain. Such modifications can prevent hypertension, lower blood

## Perspective

As primary care practitioners, we are on the front lines of hypertension treatment. To a large extent, the future well-being of our patients depends upon our ability to identify and effectively treat this common condition.

While the prevalence of hypertension in the general population is 21%, the incidence of hypertension in the population we see in the office is actually much higher due to the increased burden of disease and comorbidities. We know that almost half (43%) of patients with hypertension are undiagnosed. One of the biggest contributions that family physicians can make to society is to identify this population.

## Diagnosis

Blood pressure should be measured and recorded for virtually every adult patient at every visit. Any patient with a blood pressure at three consecutive readings greater than 140/90 mmHg should be treated aggressively, with treatment adjusted until blood pressure is below this level. In patients with diabetes, the target level is less than 130/80 mmHg.



**I**n recent years, it has been recognized that systolic blood pressure is a stronger predictor of cardiovascular disease risk than is diastolic pressure. Isolated systolic hypertension, commonly diagnosed in older patients, is a particularly hazardous condition. The relationship between blood pressure and cardiovascular disease risk is continuous, and is dependent upon the severity and duration of hypertension.

pressure, minimize the number of required antihypertensive agents, and have a positive influence upon co-existing risk factors, such as diabetes and hyperlipidemia. A successful lifestyle program requires a systematic team approach incorporating various health-care professionals, community resources and family members.

Table 4 on page 7 highlights the main recommended lifestyle modifications for all patients with hypertension as taken from JNC-VI. The need for weight loss is best determined by calculation of body mass index (BMI) rather than by measurement of weight alone and may be further refined by inclusion of waist circumference. Elevated BMI (> 27) and increased waist circumference (> 90 cm) are both closely correlated with elevated blood pressure and with increased cardiovascular mortality. Of note, increased waist circumference is also closely correlated with the metabolic syndrome, a condition that includes a variety of metabolic abnormalities, including diabetes, that together heighten the risk of CVD. Weight reduction by as little as 4.5 kg (10 lbs.) can significantly lower blood pressure and have favourable effects on glucose tolerance and lipid levels. Anorectic agents may raise blood pressure and can be associated with valvular abnormalities and pulmonary hypertension. These agents therefore should be used

with caution and only in patients with significant obesity in whom the risk:benefit ratio of using such drugs has been thoroughly evaluated.

Limitation of alcohol and dietary sodium intake may apply to subsets of patients with hypertension but may have general health benefits as well. Sodium restriction may be particularly beneficial in elderly patients, in whom salt sensitivity is common. Moderately intense physical activity on an almost daily basis can have considerable health benefits beyond lowering of blood pressure and can be accomplished by most patients in a safe and inexpensive manner. Smoking cessation is a necessary part of any lifestyle modification program that is initiated to reduce global risk of cardiovascular disease. The effect of lifestyle interventions on major cardiovascular outcomes in hypertension

remains unproven, since most clinical trials in this area were either underpowered or of insufficient duration to detect a clinically relevant effect. Furthermore, the sustainability of such interventions remains in doubt, at least based upon the same clinical trials. However, such behavioural changes should be encouraged since they are inexpensive, safe and likely to be associated with benefit.

In patients with milder degrees of hypertension without associated target organ damage or established cardiovascular disease, a trial of lifestyle modification for six to 12 months may be appropriate before initiating pharmacologic therapy. However, in patients with more severe hypertension, or those with clear evidence of target organ damage or established CVD, lifestyle and pharmacologic intervention should

be instituted in parallel and without delay (see Figure 1, page 6).

In recent years, numerous clinical trials have been completed in the arena of hypertension therapy. As a result, treatment targets have been lowered and refined based upon additional markers of risk, such as the presence of co-existing diabetes, nephropathy and congestive heart failure. The Hypertension Optimal Treatment (HOT) trial demonstrated that optimal outcomes were associated with a diastolic blood pressure of approximately 83 mmHg; in people with diabetes, the optimal DBP was even lower. In the HOT study, lowering DBP below the optimal level was not associated with any additional risk. The United Kingdom Prospective Diabetes Study (UKPDS) trial in patients with diabetes revealed that

## Treatment

There is so much literature and conflicting studies about this subject that it is necessary for family practitioners to use established and respected evidence-based guidelines for the effective treatment of hypertension. A treatment algorithm will help us to treat most of our patients. For those special cases with which we have questions or difficulty, early referral to a specialist is essential.

Treatment should begin whenever blood pressure is greater than 140/90 mmHg and continue aggressively until it is consistently below 140/90 mmHg (130/80 mmHg in patients with diabetes). Most treatments have the potential of lowering blood pressure by about 10/5 mmHg, so multiple treatments may be needed.

Do not forget to advise patients about lifestyle modification, which can be just as effective as medication. Weight loss of 4.5 kg can lower blood pressure by 10/5 mmHg, as can a reduction of alcohol intake to less than two drinks per day, or the addition of 30 minutes of aerobic exercise daily. Secondary causes of hypertension (e.g. renal artery stenosis or pheochromocytoma) should be ruled out. Treat all other modifiable risk factors such as smoking, hyperlipidemia, diabetes, nephropathy and obesity.

A diuretic such as hydrochlorothiazide or chlorthalidone (using a low dose in patients with diabetes), may be part of the antihypertensive regimen in most patients, but it does not necessarily have to be the first medication started. Other acceptable agents are ACE-inhibitors, long-acting CCBs or beta-blockers (ACE-inhibitors or ARBs in patients with diabetes). Second-line, add another agent from a different class. If goal levels of blood pressure are still not reached, add a third agent.

If blood pressure has still not reached goal, make sure you are using full therapeutic

doses, add third-line agents, or consider referral to a specialist.

It is important to involve patients in their own treatment. Encourage home blood pressure monitoring, and follow up with your patient regularly.

Generally, studies that have shown the greatest benefit with ACE-inhibitors, such as HOPE and Studies of Left Ventricular Dysfunction (SOLVD), have used doses of ACE-inhibitors at the upper end of the therapeutic range, and there have been several negative studies using low doses. It would appear reasonable to titrate up to full therapeutic dose of ACE-inhibitor, stopping the titration in the presence of adverse effects such as postural hypotension, weakness, increasing creatinine or potassium levels, or with the development of a dry annoying cough.

In the event of side-effects from ACE-inhibitors (such as cough), or where hypertension is combined with diabetic nephropathy, ARBs provide the preferred alternative. Meta-analysis of the major trials shows that the ARBs are essentially similar in their blood pressure lowering effect. The dose-response curve is fairly flat, so addition of another agent such as a thiazide is often warranted to achieve blood pressure goals.

Most ARBs are eliminated to different degrees by the kidney and the biliary system, so abnormalities in these areas may favour one drug over the other. Metabolism is generally through the cytochrome P450 (CYP450) isoenzymes 2C9 and 3A4. In elderly patients who may be taking more than one kind of medication, an ARB such as eprosarten (Teveten) offers the relief of fewer interactions with other medications as it is not metabolized by the cytochrome P450 enzyme system.

## FP Review

*Although many ARBs are metabolized via the CYP450 pathway, eprosarten is not, and is therefore an attractive option for patients susceptible to drug interactions, such as people with diabetes with nephropathy, or elderly patients who are taking a number of different medications.*

blood pressure lowering in this group of high-risk patients has a greater effect on macrovascular complications (such as cardiovascular disease) than does tight control of blood glucose.

Concomitant with the more aggressive lowering of blood pressure and global risk stratification has come the observation that most patients with hypertension require multiple drugs to achieve target blood pressure. In general, monotherapy is effective in fewer than 50% of patients with hypertension—in even fewer with more advanced hypertension. Most antihypertensive drugs lower blood pressure by 10% to 15%; thus even patients with mild hypertension will

often require more than one agent. The importance of treating isolated systolic hypertension was most emphasized by the findings in the Systolic Hypertension in the Elderly Program (SHEP) in 1991, in which lowering systolic pressure to below 160 mmHg in subjects over the age of 65 reduced cardiovascular events.

Few clinical trials have been adequately powered to demonstrate a benefit of one drug over another in preventing cardiovascular complications of hypertension. The choice of treatment in an individual patient therefore must be individualized, based upon age, ethnicity, prior side-effects and co-existing conditions. Since

hypertension is largely a silent disease, patient compliance with antihypertensive drugs remains a major challenge, particularly when multiple agents are necessary. Thus, selecting the most effective and best-tolerated drugs becomes paramount in the management of this common condition.

Most classes of drugs that lower blood pressure have proven benefits on cardiovascular outcome relative to placebo in the treatment of hypertension. Compared to placebo, diuretics and beta-blockers have been shown to lower the risk of coronary heart disease, stroke and cardiovascular mortality in relatively low-risk subjects with hypertension. Compared to

placebo, calcium-channel antagonists reduce the risk of stroke and cardiovascular death but have no significant effect upon the risk of coronary heart disease or heart failure. Angiotensin-converting-enzyme (ACE)-inhibitors reduce the risk of a variety of cardiovascular conditions as compared to placebo, most notably in the Heart Outcomes Prevention Evaluation (HOPE) study, which included high-risk patients over the age of 55. It is important to note, however, that not all patients in the HOPE study had hypertension. The newest class of agents, the angiotensin receptor antagonists (ARBs), have been shown to be very efficacious in reducing blood pressure and are well tolerated. They have demonstrated a significant advantage over placebo in patients with diabetes and various stages of nephropathy in preventing progression to end-stage renal failure. The efficacy of ARBs in reducing cardiovascular events in hypertension remains to be determined.

A more difficult question is whether antihypertensive agents differ in their ability to reduce cardiovascular events, a topic that has been the focus of considerable attention in the past several years. Several clinical trials have compared calcium channel blockers (CCBs) and/or ACE-inhibitors to diuretics or beta-blockers as the reference therapy. While none of these trials has shown convincing benefit of one class over another, either for lowering of blood pressure or for prevention of cardiovascular morbidity or mortality, they have hinted at differential benefits. For example, a meta-analysis of these trials suggests that ACE-inhibitors may be superior to CCBs in reducing the risk of congestive heart failure, whereas a CCB may be superior in reducing the risk of stroke. Compared to diuretics and beta-blockers, CCBs may not provide similar protection against coronary heart disease. The recent Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) study was a randomized comparison of the ARB losartan (Cozaar) with atenolol in hypertensive patients aged 55 or greater, all of whom had electrocardiographic evidence of left ventricular hypertrophy, placing them at increased risk of cardiovascular disease events. This study showed that despite identical reductions in systolic and diastolic blood pressure with losartan and atenolol, losartan was associated with a lower composite primary outcome of MI, stroke or cardiovascular death. The majority of this effect was driven by a 25% reduction in the risk of stroke with losartan.

Even extremely large trials of antihypertensive therapy have failed to clarify whether newer classes of drugs are clearly superior. The Anti-hypertensive and Lipid-Lowering

TABLE 3

### Components of Cardiovascular Risk Stratification in Patients with Hypertension

#### Major risk factors

- Smoking
- Dyslipidemia
- Diabetes mellitus
- Age >60 years
- Sex (men and postmenopausal women)
- Family history of cardiovascular disease: women <65 years-of-age, men <55 years-of-age

#### Target organ damage/Clinical cardiovascular disease

##### Heart diseases

- left ventricular hypertrophy
- angina/prior myocardial infarction
- prior coronary revascularization
- heart failure
- Stroke or transient ischemic attack
- Nephropathy
- Peripheral arterial disease
- Retinopathy

Adapted from: National Institutes of Health: National Heart, Lung, and Blood Institute (National High Blood Pressure Education Program). *The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure*. NIH Publication No. 98-4080, November 1997.

## FP Review

### Prognosis

Only 13% of hypertensive patients in this country are treated to goal levels, despite the fact that we are well aware that blood pressure level is a continuous risk factor for heart disease, stroke, renal failure and dementia. By effectively treating hypertension, we can reduce mortality by 20%, cardiovascular mortality by 33%, and heart attacks by 16%.

As family physicians, we have many tools in our “medical” toolbox to treat this common condition. If we cannot achieve adequate blood pressure control, the patient should be referred to a specialist.



Treatment to Prevent Heart Attack Trial (ALLHAT) was the largest randomized trial in hypertension to date. In this study, over 40,000 patients older than 55 years with hypertension and one other cardiovascular risk factor were randomized to either the diuretic chlorthalidone as the reference arm, or to an alpha-blocker (doxazosin),

dihydropyridine CCB (amlodipine), or ACE-inhibitor (lisinopril). The doxazosin arm was terminated prematurely due to poorer blood pressure control and an excess of cardiovascular events. In the final analysis, the diuretic, CCB and ACE-inhibitor were equivalent on the primary outcome of fatal coronary heart disease and non-fatal MI.

Diuretic-based therapy was slightly more effective in preventing the secondary endpoints of stroke and heart failure than the ACE-inhibitor, although the ACE-inhibitor was slightly less effective at lowering blood pressure.

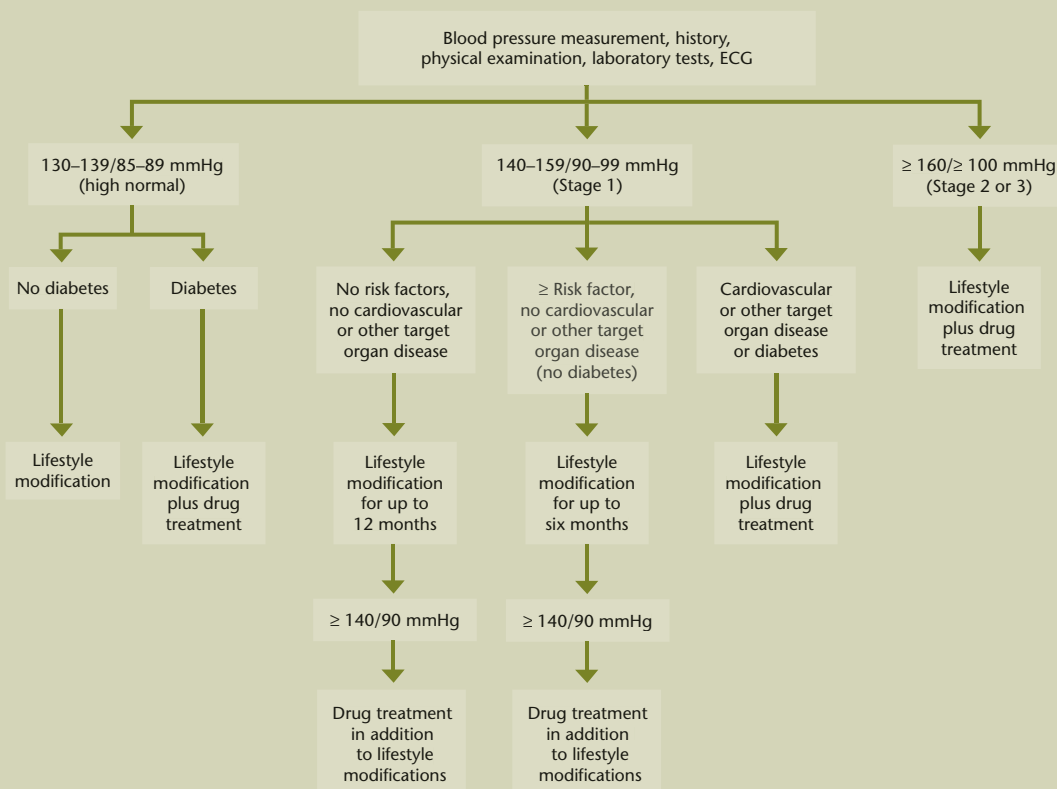
A very recent study of more than 6,000 older patients with hypertension, randomized in an open-label manner to

an ACE-inhibitor or a diuretic, showed a small but significant 11% reduction in cardiovascular events or death with the ACE-inhibitor despite identical effects upon lowering of blood pressure. In this study, there was no difference in the number of strokes in either group, and the benefit of ACE-inhibitors over diuretic was evident only in men. Most importantly, trials such as HOT and ALLHAT have confirmed the concept that multiple agents are required to achieve current target blood pressures. In these studies, an average of three drugs were required.

The current evidence points towards diuretics, beta-blockers, CCBs, ACE-inhibitors and ARBs as appropriate first-line agents in the management of hypertension. Combination therapy is increasingly the norm in the effective management of hypertension. Based upon the ALLHAT data, it would be reasonable to include a diuretic in the regimen of most patients with hypertension, which may also potentiate the effects of other drugs. In those patients with diabetes and renal disease, ACE-inhibitors or ARBs are appropriate initial therapy, as are ACE-inhibitors in patients with coronary heart disease, congestive heart failure or prior myocardial infarction. ARBs are preferred initial drugs in patients with diabetes with even early nephropathy. Where CCBs are used, only long-acting formulations should be employed, as these have been demonstrated to be safe and effective. The risk of side-effects also needs to be carefully considered when selecting antihypertensive agents, particularly for monotherapy or initial treatment (see Figure 2). Although many ARBs are metabolized via the CYP450 pathway, eprosartan is not, and is therefore an attractive option for patients susceptible to drug interactions, such as people with diabetes with nephropathy, or elderly patients who are taking a number of different medications.

FIGURE 1

## Treatment of Hypertension According to the Level of Blood Pressure and Cardiovascular Risk



Adapted from: August P. Initial Treatment of Hypertension. *NEJM* 2003;348:610-17.

FIGURE 2

## Indications for the Use of Antihypertensive Drugs, Contraindications and Side-Effects

Class of Drug	Indications	Contraindications	Side-Effects
Diuretics	Heart failure, advanced age, systolic hypertension	Gout	Hypokalemia, hyperuricemia, glucose intolerance, hypercalcemia (thiazides), hyperlipidemia, hyponatremia, impotence (thiazides)
Beta-blockers	Angina, heart failure, previous myocardial infarction, tachyarrhythmias, migraine	Asthma, chronic obstructive pulmonary disease, heart block	Bronchospasm, bradycardia, heart failure, impaired peripheral circulation, insomnia, fatigue, decreased exercise tolerance, hypertriglyceridemia
ACE-inhibitors	Heart failure, left ventricular dysfunction, previous myocardial infarction, diabetic or other nephropathy or proteinuria	Pregnancy, bilateral renal-artery stenosis, hyperkalemia	Cough, angioedema, hyperkalemia rash, loss of taste, leukopenia
Calcium-channel antagonists	Advanced age, systolic hypertension, cyclosporine-induced hypertension	Heart block (verapamil, diltiazem)	Headache, flushing, gingival hyperplasia, edema, short-acting calcium-channel antagonists may precipitate coronary ischemia
Alpha-blockers	Prostatic hypertrophy	Orthostatic hypotension	Headache, drowsiness, fatigue, weakness, postural hypotension
Angiotensin-receptor agonists	ACE-inhibitor-associated, cough, diabetic or other nephropathy or proteinuria, congestive heart failure	Pregnancy, bilateral renal-artery stenosis, hyperkalemia	Angioedema (rare), hyperkalemia

Adapted from: August P. Initial Treatment of Hypertension. *NEJM* 2003;348:610-17.

### PROGNOSIS

Hypertension is increasingly prevalent in our society and is often associated with co-existing cardiovascular risk factors. A comprehensive risk-stratification and treatment strategy is required to optimally manage patients with this condition. Lifestyle interventions, though difficult to initiate and maintain, can have considerable benefits on lowering blood pressure and controlling other risk factors. To reduce cardiovascular morbidity and mortality, pharmacologic treatment is usually required, often with multiple agents to achieve target blood pressures, which may differ between patients based upon co-existing conditions. Current

evidence suggests that targeted combination therapy, often incorporating low-dose diuretic therapy, can improve cardiovascular outcomes in the majority of patients.

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TABLE 4

## Lifestyle Modifications for Hypertension Prevention and Management

- Lose weight if overweight.
- Limit alcohol intake: no more than 1 oz. (30 mL) ethanol (e.g. 24 oz. [720 mL] beer, 10 oz. [300 mL] wine, or 2 oz. [60 mL] 100-proof whiskey) per day or 0.5 oz. (15 mL) ethanol per day for women and lighter-weight people.
- Increase aerobic physical activity (30–45 minutes most days of the week).
- Reduce sodium intake to no more than 100 mmol per day (2.4 g sodium or 6 g sodium chloride).
- Maintain adequate intake of dietary potassium (approximately 90 mmol per day).
- Maintain adequate intake of dietary calcium and magnesium for general health.
- Stop smoking and reduce intake of dietary saturated fat and cholesterol for overall cardiovascular health.

Adapted from: National Institutes of Health: National Heart, Lung, and Blood Institute (National High Blood Pressure Education Program). *The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure*. NIH Publication No. 98-4080, November 1997.

## RESOURCES

■ **CANADIAN DIABETES ASSOCIATION**

The CDA is the largest non-governmental supporter of diabetes research, education and advocacy. Formed in 1953, the association comprises 150 branches across the country. Guidelines on hypertension in diabetes can be found on the Web site, along with information on diabetes programs, services and advocacy for both patients and professionals. Visit: [www.diabetes.ca](http://www.diabetes.ca)

■ **DIABETES CLINIC**

Diabetes Clinic is independent medical clinic specializing in the treatment of diabetes mellitus according to the treatment guidelines of the Canadian Diabetes Association. The Web site, which is aimed at people with diabetes and the physicians who treat them, offers patient tools and information on medications, research and insulin pumps, with sections on hypertension in diabetes. Visit: [www.diabetesclinic.ca](http://www.diabetesclinic.ca)

■ **NATIONAL INSTITUTES OF HEALTH**

*The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-VI)* is available through the NIH's National Heart, Lung and Blood Institute Web site. Health information, scientific resources, information on research funding and clinical guidelines can also be found at this site. Visit: <http://www.nhlbi.nih.gov/guidelines/hypertension/jnc6.pdf>

■ **THE CANADIAN HYPERTENSION SOCIETY**

The CHS was established in 1979 by a group of Canadian health professionals interested in improving hypertension research, education and patient care. Their mission is to promote the prevention and control of hypertension through, fostering effective approaches for the hypertension management in Canada, encouraging and co-ordinating of research on hypertension in Canada, providing a forum for the presentation of hypertension research, circulating information about hypertension to health

professionals and the public, and co-operating with other associations with interests in hypertension. The Web site provides numerous links for physicians. Visit: [www.chs.md](http://www.chs.md)

■ **THE CANADIAN JOURNAL OF CARDIOLOGY**

A summary of *The 2000 Canadian Hypertension Recommendations* from the Canadian Hypertension Recommendations Working Group can be found at this Web site. The description covers diagnosis, laboratory tests, treatment and target values. Visit: [www.pulsus.com/cardiol/17\\_05/cmbe\\_ed.htm](http://www.pulsus.com/cardiol/17_05/cmbe_ed.htm)

■ **THE CANADIAN MEDICAL ASSOCIATION**

The CMA Web Site requires authorized access for weekly news, featured services and member benefits for physicians. A section on Clinical Practice Guidelines will help you keep up-to-date on the latest recommendations. Visit: [www.cma.ca](http://www.cma.ca)

■ **THE GUIDELINES ADVISORY COMMITTEE**

Authorized by the Ministry of Health and Long-Term Care and the Ontario Medical Association, the GAC promotes evidence-based health care in Ontario by encouraging physicians to use the best available clinical practice guidelines. The GAC endorses each recommended guideline following an in-depth review. Summaries of the guidelines rated most highly and links to all available guidelines are provided on the Web site. Visit: [www.gacguidelines.ca](http://www.gacguidelines.ca)

■ **THE HEART & STROKE FOUNDATION**

The mission of the foundation is to improve the health of Canadians by preventing and reducing disability and death from heart disease and stroke through research, health promotion and advocacy. The Web site includes interactive blood pressure management tools and information for patients such as "Your Blood Pressure Action Plan" and a risk assessment questionnaire for developing high blood pressure. Visit: [www.heartandstroke.ca/bloodpressure](http://www.heartandstroke.ca/bloodpressure)

# 1 Case Study: Presentation

**A 64-YEAR-OLD MAN WHOSE PREVIOUS FAMILY DOCTOR RETIRED RECENTLY. HE IS A NEW PATIENT TO YOU.**

**This man is married and runs a printing company. He was diagnosed with type 2 diabetes about eight years ago. He is a lifetime non-smoker and he says he was told by his former family physician that his cholesterol was “okay”. In the past year, he has had high blood pressure, which has been attributed to the stresses of running his own business.**

## PATIENT HISTORY

This patient's family history is unremarkable. He has osteoarthritis, which causes mild discomfort in his knees and also suffers from heartburn. He drinks two to three alcoholic beverages per day. He denies any history of exertional chest pain, but he does admit to mild dyspnea with usual activities. His current medications include metformin 500 mg twice per day, ibuprofen 600 mg four times per day, and omeprazole 20 mg once per day.

## EXAMINATION

On examination, he appears mildly overweight. His body mass index is 29. Blood pressure is 160/100 mmHg bilaterally, measured twice during the visit. Heart rate is regular at 78 bpm. His fundi exhibit early arteriolar narrowing without exudates or hemorrhages. His carotid pulses and JVP are normal. Lungs are clear with an apical fourth heart sound and no murmurs. There are no abdominal masses or bruits. His distal pulses are weakly palpable with no edema.

## ASSESSMENT

This man has mild-to-moderate hypertension, type 2 diabetes, and is overweight. As such, he is at very high risk for developing atherosclerosis in the form of coronary, cerebrovascular or peripheral vascular disease. Additionally, he has a fourth heart sound and reduced peripheral pulses, with early hypertensive retinopathy. Finally, he complains of exertional dyspnea, which may be due to hypertensive heart disease or myocardial ischemia.

## MANAGEMENT

This patient warrants aggressive investigation and management of all of his vascular risk factors, including his hypertension. He should be counselled regarding the benefits of moderate alcohol consumption, weight loss and regular aerobic exercise. He should have assessment of electrolytes, diabetic control, renal function, urine microalbumin and a fasting lipid profile. As well, he should have an ECG and an echocardiogram to look for left ventricular hypertrophy and diastolic dysfunction, given his exertional dyspnea and fourth heart sound.

If the patient can tolerate it, his ibuprofen should be reduced or ideally replaced with acetaminophen, since NSAIDs can exacerbate hypertension and induce renal insufficiency in diabetics. He should be started on antihypertensive therapy, in this case with either a thiazide diuretic or a drug that manipulates the renin-angiotensin system, such as an ACE-inhibitor or an ARB. He should also be told that it is highly likely he will require multiple medications to bring his blood pressure to the recommended target of 130/80 mmHg for someone with diabetes and to 125/75 mmHg if he turns out to have renal disease.

## FOLLOW-UP

The patient stops the ibuprofen and is started on hydrochlorothiazide 25 mg once per day as well as ECASA 81 mg once per day. He begins lifestyle changes. His ECG is normal, but his echo shows mild concentric LVH with mild diastolic dysfunction. His creatinine is 130 mmol/L with an elevated microalbumin level. His fasting LDL cholesterol is 3.8 mmol/L with normal TG and HDL.

At his next visit, his BP is 144/94 mmHg.

## COMMENTARY

This man has persistent hypertension despite his diuretic and has diabetes with early nephropathy. At this point, an ACE-inhibitor or ARB should be added, along with an HMG-CoA-reductase inhibitor (statin) dosed to achieve a fasting LDL of <2.5 mmol/L. If on maximal dose of ACE-inhibitor/ARB his blood pressure remains above 125/75 mmHg, a dihydropyridine CCB should be added. ●

# 2 Case Study: Presentation

**A 76-YEAR-OLD WIDOW WHO LIVES ALONE.**

**Once a regular patient of yours, she stopped coming in to the office about two years ago after her husband passed away. She has now come to you for a general assessment.**

## PATIENT HISTORY

She has at least a 12-year history of hypertension and is a non-diabetic. She is a non-smoker and non-drinker. She is unaware of her lipid status. Her family history reveals that her mother died at age 74 of a stroke. She has had several minor surgical procedures in the past. Her medications include hydrazide 25 mg once per day, paroxetine 20 mg once per day (started after her husband's death) and atorvastatin 20 mg at bedtime.

She generally feels well, though complains of occasional headaches without visual disturbance. She has no exertional chest pain or dyspnea.

## EXAMINATION

On examination, she looks well and is fairly slim. Blood pressure is 150/90 mmHg measured twice, with no significant difference between arms. Her fundi are difficult to visualize due to early cataracts, but are likely normal. She has no vascular bruits. There is a grade 2/6 early systolic ejection murmur at the base of the heart, with normal heart sounds and no diastolic murmur. The abdomen is benign. Distal pulses are normal with no edema.

## ASSESSMENT

This is an elderly patient with uncontrolled hypertension despite being on a diuretic. She is asymptomatic and is being treated for hypercholesterolemia as well. As such, she is at moderate risk for cardiovascular disease. Isolated systolic hypertension in the elderly is a particularly strong risk factor for stroke. Her systolic murmur is likely benign and due to aortic valve sclerosis related to her hypertension.

Her target blood pressure should be below 140/90 mmHg. She should have an assessment of electrolytes, renal function and urine microalbumin, a fasting lipid profile and an ECG. She should be counselled regarding the benefits of lifestyle interventions in assisting with the pharmacologic management of her hypertension.

## MANAGEMENT

At her next visit, this patient's blood pressure is 162/84 mmHg with no change in her medications. Her ECG shows 1 mm ST depression in the lateral leads, with voltage for LVH. Her creatinine is normal, but her microalbumin level is elevated. Her fasting LDL is 3.4 mmol/L, with normal HDL and TG.

At this stage, the addition of a second antihypertensive agent should be considered, particularly a CCB or an ACE-inhibitor/ARB. Given the presence of LVH on her ECG, it may be prudent to add an ARB, which was shown to be superior to a beta-blocker in the prevention of stroke in subjects with hypertension and LVH in the recent LIFE trial. Since several ARBs are metabolized by the CYP450 enzyme pathway and the patient is already on paroxetine, eprosartan, which is a known inhibitor of this pathway, may be appropriate because it is less likely to be metabolized via CYP450. In addition, she should be started on ECASA 81-325 mg once per day. ●

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