

Antihypertensives: A Drug Review

This article describes the relevant pharmacology of all major classes of antihypertensive drugs, along with the rationale behind their use in combination and ways to avoid side effects in their use.



By Caren Wu, MD, FRCPC; Tara Cowtan, MD, FRCPC; and Norman RC Campbell, MD, FRCPC

The approach to treatment of hypertension has evolved over the last few years, given new agents and evidence from recent antihypertensive drug trials. The aim of this review is to summarize risk stratification for purposes of initiating treatment, to review current Canadian treatment guidelines, and to briefly describe

recent clinical trials that have added knowledge to the initial approach in the treatment of hypertension.^{1,2} In addition, we describe the recommended first-line antihypertensive drug classes, their current role in the treatment of hypertension, use in combination, and ways to avoid side effects.

About the authors...

Dr. Wu is clinical scholar in the general medicine division, the University of Calgary, Alberta.

Dr. Cowtan is staff physician in the general medicine division, Foothills Hospital, Calgary, Alberta.

Dr. Campbell is professor of medicine, divisions of general internal medicine and geriatrics, departments of pharmacology and therapeutics, Cardiovascular Research Group, faculty of medicine, the University of Calgary, Alberta.









Risk Stratification

Risk stratification enables one to assess prognosis in a patient, as well as choosing the most appropriate approach to treatment. When assessed, the vast majority of hypertensive patients have additional cardiovascular risks. A global cardiovascular risk assessment is better than estimating risk based on blood pressure (BP) alone and can be used to inform patients and customize their treatment plans. A recent study revealed the use of a

Antihypertensives

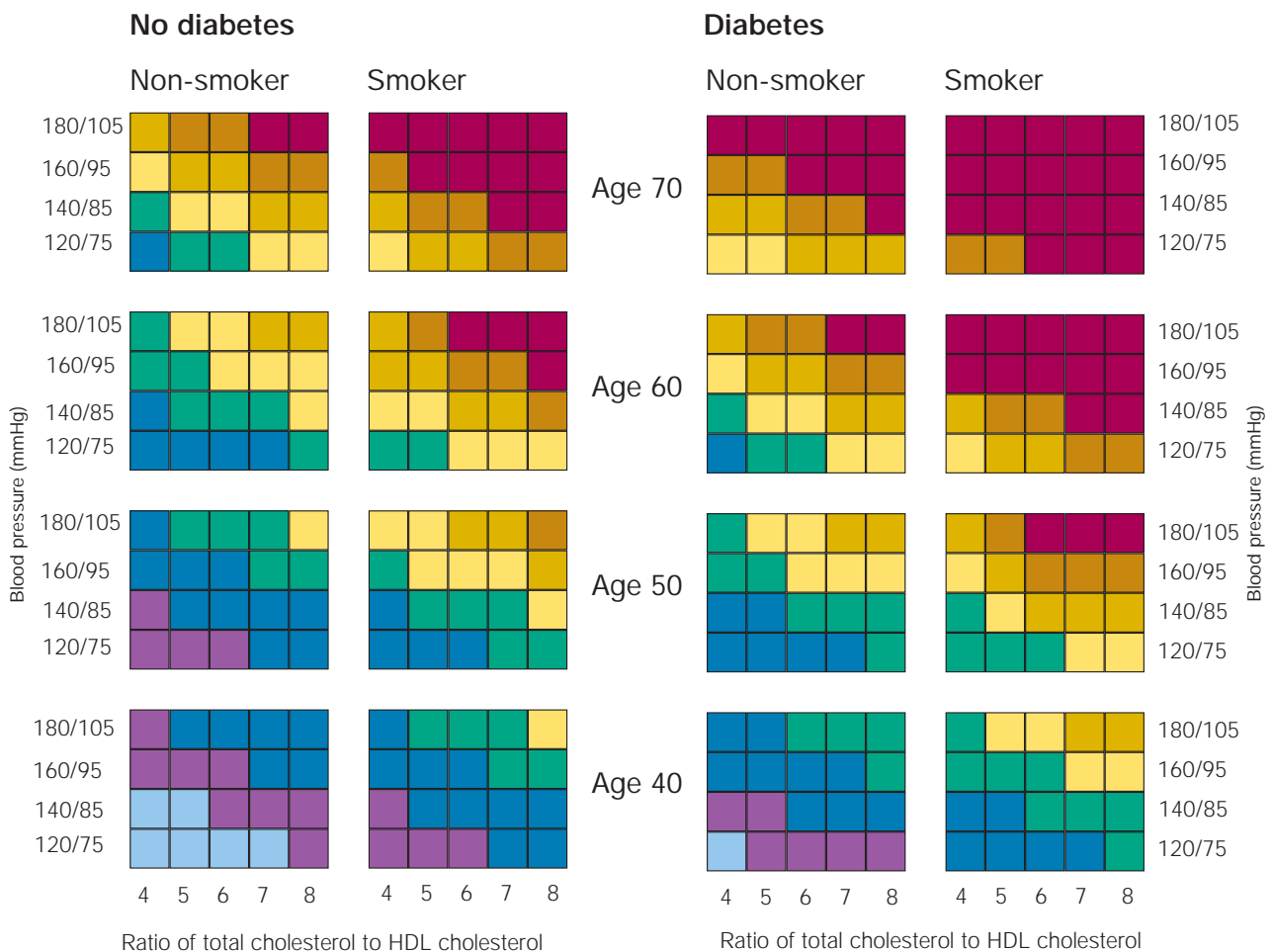
Table 1

New Zealand Cardiovascular Risk Prediction Charts

	Risk level 5 year cardiovascular risk (non-fatal and fatal)	Benefit (1) Cardiovascular events prevented per 100 treated for 5 years*	Benefit (2) Number needed to treat for 5 years to prevent 1 event*
Very high	 > 30%	> 10	< 10
	 25% to 30%	9	11
	 20% to 25%	7.5	13
High	 15% to 20%	6	16
Moderate	 10% to 15%	4	25
	 5% to 10%	2.5	40
Mild	 2.5% to 5%	1.25	80
	 < 2.5%	< 0.8	> 20

*Based on a 20% reduction in total cholesterol or a reduction in blood pressure of 10-15 mmHg systolic or 5-8 mmHg diastolic, which reduces risk of cardiovascular disease by about one-third over five years.

Men



This guide provides a simple quantitative method for assessing a person's risk of cardiovascular disease and the likely benefits of lowering BP with drugs.

Using the charts

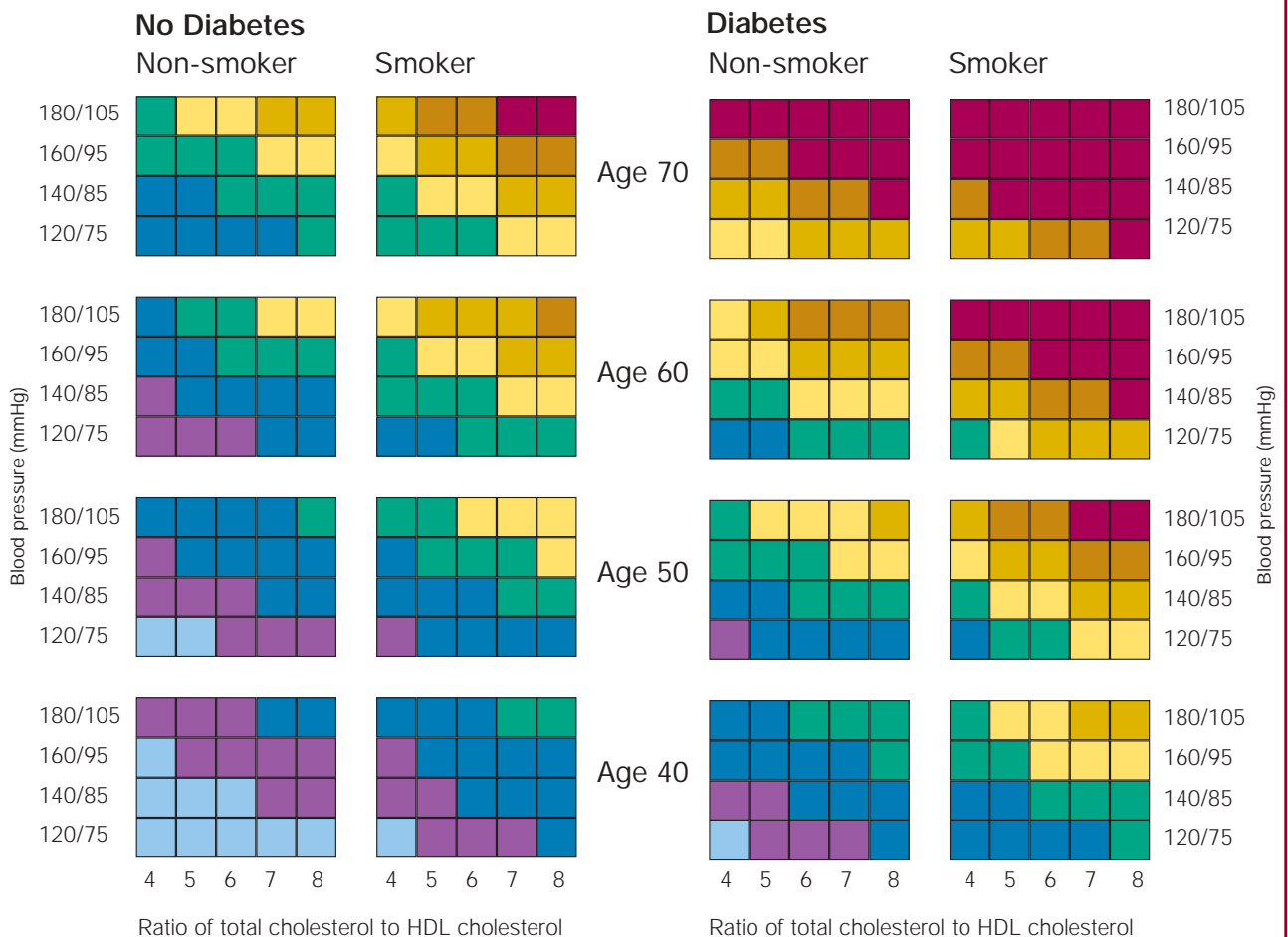
Choose the chart section relating to the person's sex, diabetic status, smoking status, age (*i.e.*, use age category of 60 years for people aged 55 to 65).

Find the cell nearest to the person's BP and ratio of total cholesterol to HDL cholesterol (when SBP and DBP fall in different categories, the higher category applies).

Compare the colour of the cell with the risk level colour key and estimate the five-year risk of cardiovascular disease.

The chart also indicates the number of cardiac events prevented per 100 patients treated, as well as the number of patients needed to be treated for five years to prevent one cardiovascular event.

Women





Lifestyle modifications may prevent or delay the need for pharmacotherapy and, in addition, have been shown to enhance the effectiveness of concomitant BP-lowering medication.

risk chart was associated with greater reductions in systolic blood pressure (SBP).³ Patients may respond more favourably to their prescribed regimen when they have knowledge of their own personal risk of cardiovascular events.

There are various methods of risk stratifying. A reasonable approach would be to use

risk charts that can also be used as a patient education tool. Table 1 is the New Zealand cardiovascular risk prediction chart.⁴ These guidelines must be used with some caution among young individuals (i.e., age < 40), in whom long-term cardiovascular risks are more relevant, in those with non-traditional risk factors and in those with established vascular disease.

Risk stratification can guide management decisions, particularly with regards to initiating pharmacotherapy. Current recommendations indicate that low-risk patients with a diastolic blood pressure (DBP) of < 100 mmHg do not need to be started on any pharmacotherapy.^{1,2} It is important that these patients are the exception, rather than the rule. Hypertension, in general, is a metabolic disorder that occurs in conjunction with other cardiovascular risks. Drug therapy is recommended for most people with diastolic readings of \geq 90 mmHg or systolic readings of \geq 160 mmHg.

When a patient has hypertension and one or more risk factors or evidence of target organ damage, this worsens his/her prognosis. Drug therapy should be initiated, in addition to modification of his/her other risk factors. Recent trials suggest high-risk patients with stroke, ischemic heart disease, or diabetes, plus one other risk factor, should be treated to lower BP and prevent cardiovascular events, even those considered to be normotensive.^{5,6}

Regardless of the necessity for drug therapy, patients with hypertension should be encouraged to pursue the following lifestyle modifications:

- Healthy diet (high in fresh fruit, vegetables and low-fat dairy products and low in saturated fat);

Table 2

Considerations in the Individualization of Antihypertensive Therapy

Condition	Initial Therapy	Second-line Therapy	Notes/Cautions*
Uncomplicated hypertension	Low-dose thiazide-like diuretics, beta blockers, ACE inhibitors or long-acting dihydropyridine CCBs	Combinations of first-line drugs.	Alpha blockers are not recommended as first-line therapy. Beta blockers are not recommended as first-line therapy in those > age 60. Hypokalemia should be avoided by using K sparing agents in those prescribed thiazides
Isolated systolic hypertension in the elderly	Low-dose, thiazide-like diuretics, or long-acting dihydropyridine CCBs		Hypokalemia should be avoided by using K sparing agents in those prescribed thiazides
Dyslipidemia	As for uncomplicated hypertension	As for uncomplicated hypertension	Beta blockers (non-ISA) are not recommended as first-line therapy
Angina or prior MI	Beta blockers, ACE inhibitors	Long-acting CCBs	
Systolic dysfunction	ACE inhibitors (beta blockers, thiazide or loop diuretics, and/or spironolactone as additive therapy)	ARBs, hydralazine/isosorbide dinitrate, long-acting dihydropyridine CCBs	Non-dihydropyridine CCBs are not recommended
Left ventricular hypertrophy	As for uncomplicated hypertension	As for uncomplicated hypertension	Hydralazine or minoxidil are not recommended
Renal disease	ACE inhibitors (diuretics as additive therapy)	Combinations of other agents	
Renovascular disease	As for uncomplicated hypertension	As for uncomplicated hypertension	Caution in the use of ACE inhibitors or ARBs
Diabetes mellitus without nephropathy	ACE inhibitors	Cardioselective adrenergic antagonists, thiazides (low doses), long-acting CCBs, or ARBs	
Diabetes mellitus with nephropathy	ACE inhibitors, ARBs	Cardioselective beta blockers, low-dose thiazide diuretics, or long-acting CCBs	If the serum creatinine is > 150 µmol/L, consideration should be given to replacing a thiazide with a loop diuretic for volume control
Diabetes mellitus with isolated systolic hypertension	Low-dose thiazide diuretics, long-acting dihydropyridine CCBs, ACE inhibitors)		

*Short-acting CCBs are not recommended.

ACE: angiotensin converting enzyme CCB: calcium channel blocker K: potassium ARB: angiotensin receptor blocker
ISA: intrinsic sympathomimetic activity

- Avoidance of salty foods and salt additives;
- Moderation or abstinence from alcohol;
- Weight reduction in those overweight; and
- Regular physical activity.

Lifestyle modifications may prevent or delay the need for pharmacotherapy and, in addition, have been shown to enhance the effectiveness of concomitant BP-lowering medication.

Canadian Guidelines

The management of hypertension includes careful diagnosis and screening for secondary causes of hypertension, assessment of risk factors, and choice of appropriate lifestyle and pharmacological approaches to treatment.

Once a patient has been definitively diagnosed as hypertensive, treatment guidelines are straightforward. Some adjustments for individual needs is required, depending on co-morbid conditions (Table 2).

There are some caveats to treatment. Alpha blockers are not recommended as first-line agents for uncomplicated hypertension and beta blockers are not recommended as first-line agents in those aged > 60. Both types of drugs may play a role in combination therapy or when other comorbid conditions co-exist. Short acting calcium channel blockers are not indicated in the treatment of hypertension. For those patients with elevated serum creatinine > 150 $\mu\text{mol/L}$, a thiazide diuretic has a limited effect on vascular vol-

ume, and a loop diuretic (i.e., furosemide) is usually required.

Target Levels for Uncomplicated Hypertension

Goals of therapy for uncomplicated hypertension are a BP level of < 140/90 mmHg.

Brief Overview of Recent Important Trials
New evidence for hypertension control in stroke patients has been published recently in the Perindopril Protection Against Recurrent Stroke Study (PROGRESS). Previously, the effectiveness of antihypertensive agents for secondary prevention of cerebrovascular disease was uncertain.

This large trial randomized individuals with a history of stroke or transient ischemic attack (TIA) in the past five years to therapy (perindopril, an angiotensin converting enzyme [ACE] inhibitor — with or without indapamide, a diuretic) or placebo. Both hypertensive and non-hyper-

tensive patients were enrolled. The risk of stroke and cardiovascular events in this high-risk group were reduced in both hypertensive and normotensive patients to the same extent, as predicted by the degree of BP reduction.⁶

Angiotensin II receptor blockers (ARBs) are considered an alternative management option in hypertension, especially when ACE inhibitors are strongly indicated, but not tolerated. Two randomized, placebo-controlled trials, published in 2001, demonstrated a renoprotective effect of ARBs (losartan and irbesartan) in patients with diabetic nephropa-



thy.^{7,8} Both drugs were effective in reducing the composite end point of death, dialysis or doubling of serum creatinine, compared to conventional treatment (that excluded ACE inhibitors).

Recently, the Losartan Intervention For Endpoint reduction in hypertension (LIFE) trial demonstrated an ARB (losartan) was superior in preventing cardiovascular events and produced fewer adverse effects than a beta blocker (atenolol), among older diabetic and non-diabetic patients with hypertension and left ventricular hypertrophy.^{9,10} Both drug regimes equally lowered BP. While highly positive from both a clinical and statistical perspective, the trial requires careful interpretation. In older patients, beta blockers are inferior to diuretics and are not recommended as first-line therapy. This will generate debate about the application of the results of this otherwise very high quality study. At a minimum, the trial confirms the wisdom of not prescribing beta blockers as first-line therapy for primary prevention in older patients.

The recommendation that alpha blockers are not recommended as initial therapy stems from early adverse results from the doxazosin arm in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). The doxazosin arm of the trial was prematurely discontinued because of an increased risk for a number of cardiovascular end points, including a doubling of the risk of congestive heart failure relative to chlorthalidone, a diuretic. This study, therefore, provides strong evidence for not using alpha blockers as first-line agents in the treatment of hypertension.¹¹

Role of Available Drugs: Indications, Precautions, Side Effects

Many believe low to moderate doses of diuretics and beta blockers are associated with compromised quality of life and common side effects. Unfortunately, this myth is perpetuated by many, despite high quality randomized trials that indicate this is not the case. The Department of Veteran Affairs Cooperative Study revealed that, in the treatment of stage I and stage II hypertension in men, hydrochlorothiazide, atenolol, captopril and long-acting diltiazem had similar rates of adverse events in treatment groups, compared to placebo, after one year of follow-up.¹² Prazosin and clonidine had higher adverse effect rates.

The Treatment of Mild Hypertension Study (TOMHS) allocated men and women aged 45 to 69 to chlorthalidone, acebutolol, doxazosin, amlodipine, enalapril or placebo in the treatment of mild hypertension. The study found increased quality of life in two of the treatment groups (atenolol, chlorthalidone), compared to placebo, and similar rates of side effects among all the groups (compared to placebo) after four years of follow-up.¹³

The relationship between therapy intensity and quality of life was investigated in a sub-study from the Hypertension Optimal Treatment (HOT) Study.¹⁴ The purpose of this study was to investigate the association between targeted levels of DBP (90, 85, 80) with quality of life. The antihypertensives used in the study included felodipine initially, and then the addition of other drug

classes (including beta blockers, ACE inhibitors or diuretics) to reach target DBP levels. It was found that the greater the reduction in DBP, the greater the improvement in quality of life. Intensified therapy, however, was associated with some increase in side effects, particularly with respect to the use of diuretics and decreased sexual function.

That patients and physicians believe side effects are commonly associated with antihypertensive therapy is not debatable. In the Systolic Hypertension in the Elderly Program (SHEP), side effects occurred in just over 90% of the active treatment group.¹⁵ However, these were generally symptoms associated with daily living and occurred in just under 90% of the placebo group.¹⁵ This false perception is aggravated by the misleading material on side effects that are commonly handed out to patients by pharmacies and to health-care professionals in product monographs (included in the Compendium of Pharmaceuticals). Commercial continuing medical education events commonly have speakers that promote newer products that have placebo-like, side-effect profiles and quality of life changes, without recognizing or even contradicting the fact that older drug classes have the same side-effect profile as placebo at moderate doses.

Diuretics

Diuretics have been shown to be effective in decreasing cardiovascular morbidity and all-cause cardiovascular mortality. Diuretics are one of the recommended first-line choices for uncomplicated hypertension. They show excellent efficacy in treating

isolated systolic hypertension in the elderly. Black people also show a good response to monotherapy with diuretics in reducing systolic hypertension, as compared to other major drug classes.¹²

Thiazide-like diuretics are the diuretic of choice and act on the distal convoluted tubule by inhibiting sodium co-transport. Chlorthalidone and indapamide have a similar mechanism of action. Potassium-sparing diuretics are rarely used in isolation for their antihypertensive effect, but should be used to decrease the incidence of hypokalemia with thiazide diuretics. Loop diuretics, such as furosemide, are seldom used unless there is significant co-morbid renal dysfunction or treatment-resistant hypertension.

Use of diuretics can be associated with hypokalemia that has been shown to be connected with poorer cardiac outcomes.^{1,2} It is suggested that a thiazide diuretic be used in combination with a potassium-sparing diuretic (spironolactone/amiloride/triamterene) to counter this effect. Thiazide diuretics may also exacerbate gout. In addition, spironolactone may cause breast tenderness in women and gynecomastia and erectile dysfunction in men.

Some concern is raised about an increase in sexual dysfunction with the use of diuretics. Past studies may have shown unfavorable associations, perhaps due to confounding with age and disease itself.¹³ About 12% of middle-aged hypertensive men have erectile dysfunction, a number that increases to 14% with diuretic therapy. Lowering BP levels may cause erectile dysfunction, regardless of the medication.¹³

Beta Blockers

Beta-adrenergic blockers are a good choice for initial therapy in uncomplicated hypertension. They also are indicated specifically in the setting of hypertension associated with stable angina, systolic dysfunction or post-myocardial infarction (MI). However, they are not as effective in primary prevention of cardiovascular events as diuretics for those aged > 60 and, therefore, are not indicated as first-line therapy in this age group.

All beta-adrenergic blockers are roughly equivalent in antihypertensive effect, but may vary in side-effect profile, depending on cardio-selectivity. Beta-1 selective agents have less effect on lipid profile and glucose metabolism than non-selective agents. Intrinsic sympathomimetic activity (ISA), such as with acebutolol, causes less bradycardia or derangement of blood lipids. Drugs that are selective for beta-1 receptors may cause less bronchospasm, but it is important to note any beta blocker can cause acute bronchospasm in an asthmatic patient. No beta-adrenergic antagonist is purely cardio-selective.¹⁶

Other side effects of beta-adrenergic blockers include decreased maximal exercise capacity, as well as weight gain (although their use in mild to moderate hypertension has been associated with increased quality of life, as compared to placebo).¹³ Beta-adrenergic antagonists may cause a withdrawal syndrome when discontinued. They also can precipitate ischemia among



ACE inhibitors are appropriate first-line antihypertensives and are specifically recommended initial therapy in patients who have hypertension associated with diabetes, recent MI, systolic dysfunction, or renal disease.

those with coronary artery disease when stopped. Therefore, it is better to taper off the drug dosage before discontinuation.

ACE Inhibitors

ACE inhibitors are appropriate first-line antihypertensives and are specifically recommended initial therapy in patients who have hypertension associated with diabetes, recent MI, systolic dysfunction, or renal disease.

ACE inhibitors are usually well tolerated and may provide protective effects to those with renal insufficiency (particularly diabetic nephropathy) as well as various cardiac conditions, such as heart failure and MI.

Case Discussion

A reasonable option would be to consider raising the dose of the hydrochlorothiazide to 25 mg. If there is inadequate response to this dose, then adding another drug in combination is now the preferred course, rather than switching medications. Most patients eventually require more than one medication for control of their hypertension. Of note, increasing the thiazide dose may cause hypokalemia. Further increases in the dose of hydrochlorothiazide will usually have little additional hypotensive effect, except in volume-dependant hypertension resistant to several medications.

A second agent in combination could either be a beta blocker or an ACE inhibitor. Both of these drugs have a synergistic effect with thiazide diuretics. Ramipril 2.5 mg a day is prescribed and titrated up over the next few months.

If Greg's BP is still difficult to control, compliance issues and secondary hypertension must be considered.

ACE inhibitors produce a dry, hacking cough in about 5% of patients. This needs to be differentiated by the cough that occurs in almost 10% of placebo-treated patients. The cough usually disappears a couple of weeks after discontinuation and recurs with rechallenge. Angioedema is a rare, but potentially life-threatening, adverse reaction associated with the use ACE inhibitors.

Hyperkalemia can occur during ACE inhibitor therapy. This usually involves those taking potassium or other potassium-sparing agents, those with renal dysfunction or those with diabetes and high potassium levels. Caution also needs to be used in the treatment of patients with bilateral renovascular disease or those who are volume depleted when use of an ACE inhibitor may precipitate renal failure.

A routine check of the serum creatinine at one-week and one-month post-initiation of therapy will verify there is no hyperkalemia or associated worsening renal dysfunction. The latter may be a clue to bilateral renal artery stenosis. I warn patients to stop ACE inhibitors if they develop severe diarrhea or vomiting. Finally, ACE inhibitors are teratogenic and are contraindicated in pregnancy.

ARBs

ARBs are not yet recommended as initial therapy for uncomplicated hypertension, but in the setting of intolerance of ACE inhibitors, they are a good alternative for those with systolic dysfunction and diabetic nephropathy. The recent positive results from the LIFE trial have not yet been considered in the development of treatment recommendations.¹⁰

The AII receptor blockers displace AII from its specific AT1 receptor, resulting primarily in a fall in peripheral resistance.

There is little difference in antihypertensive effect between ARBs and ACE inhibitors, but further studies are required to ascertain their equivalency in reducing cardiovascular complications.

ARBs have the advantage of not producing the side effect of cough. The same precautions need to be taken as with ACE inhibitors, with respect to hyperkalemia and worsening renal dysfunction in bilateral renal artery stenosis or dehydration.

ARBs are also contraindicated in pregnancy.

Table 3

Additive Hypotensive Effect

For additive hypotensive effect in dual therapy, combine an agent from column 1 with any in column 2*:

Column 1

Low-dose thiazide diuretic
Long-acting dihydropyridine CCBs

Column 2

Beta blocker
ACE inhibitor**

* Dual combination of agents within column 1 and within column 2 have less than additive hypertensive effect, but may be indicated in specific settings (*i.e.*, column 2 drugs in patients following myocardial infarction.)

** Angiotensin receptor blockers are an alternative initial choice in patients with diabetes and nephropathy.
ACE: angiotensin converting enzyme inhibitor CCB: calcium channel blocker

CCBs

CCBs can be divided into two main groups — verapamil and diltiazem — which possess depressive effects on cardiac contractility and atrio-ventricular conduction, as well as inducing vasodilatation versus the dihydropyridine CCBs. First-generation dihydropyridine CCBs, such as nifedipine, have some minor effects on cardiac contractility. Second-generation dihydropyridine CCBs, however, such as amlodipine and felodipine, have almost pure vascular-selective vasodilator effects.

Long-acting dihydropyridine CCBs can be used as first-line agents or, in combination, to achieve additive effects with other agents. The elderly with isolated systolic hypertension, as well as black individuals, have been noted to be particularly responsive to CCBs.¹² Notably, there is additional antihypertensive effect found when a dihydropyridine is added to verapamil or diltiazem.

Short-acting CCBs should not be prescribed in the treatment of hypertension. Diltiazem and verapamil should be avoided in patients with sick sinus syndrome, second- or third-degree heart block, and congestive heart failure. Constipation is common with verapamil. With dihydropyridines, most side effects are related

to the vasodilator effects (*i.e.*, headaches, flushing, local ankle edema). Combining a dihydropyridine CCB with an ACE inhibitor may help to reduce pedal edema.

Use of Combination Therapy

Monotherapy controls BP in approximately one-half of those with stage I hypertension; the remainder require some form of combination treatment. After a trial of therapy with one of the recommended initial first-line agents, patients will either have their dosage increased, another drug substituted or a second drug added to their treatment.

With the latter approach, it is useful to block the compensatory mechanisms that may counter the effectiveness of the first medication. Rational combinations of two moderately dosed drugs are superior in BP lowering efficacy, as compared to one drug which is maximally-dosed. In general, combinations have less side effects.¹⁷ Some combinations of antihypertensive drugs have an additive hypotensive effect, while others have a less-than-additive effect. Table 3 illustrates combinations of first-line therapies that have additive effects.


Some combinations have strong indications, regardless of BP effects (i.e., beta blockers and ACE inhibitors post-MI and in systolic dysfunction).

If there is only partial response to dual therapy, then triple or quadruple combinations with any of the first-line agents should be effective. When a patient appears resistant to a multiple-drug regimen, re-evaluation for non-compliance, drug interactions and secondary causes of hypertension should be considered. Referral of patients with resistant hypertension to a specialist is at the discretion and comfort level of the treating physician.

Rational combinations of two moderately dosed drugs are superior in BP lowering efficacy, as compared to one drug which is maximally-dosed.

Conclusion

The management of hypertension begins with risk assessment to determine prognosis and approach to treatment. Once a patient's risks are assessed, it is determined whether he/she requires pharmacological treatment, in addition to lifestyle modification. If drug therapy is indicated, in addition to lifestyle changes, the choice of initial drug is based on co-morbid conditions and risk factors.

We have briefly outlined the approach recommended in the current Canadian treatment guidelines. The relevant pharmacology of the major classes of antihypertensive drugs has been described, along with the rationale behind their use in combination and ways to avoid side effects in their use. 

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