

Report of the Canadian Hypertension Society Consensus Conference: 3. Pharmacologic treatment of essential hypertension

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Résumé : Les auteurs examinent des preuves récentes au sujet du rôle des diurétiques thiazidiques et des β -bloquants dans la monothérapie de l'hypertension essentielle. Les α -bloquants, les médicaments à action centrale, les inhibiteurs de l'enzyme de conversion de l'angiotensine et les antagonistes du calcium sont également débattus. Des recommandations sont faites sur le traitement pharmacologique de l'hypertension non compliquée (les diurétiques thiazidiques ou les β -bloquants demeurent les médicaments de choix) et de l'hypertension chez les patients atteints ou à risque de maladie cardiovasculaire, de lésion des organes cibles, de maladie pulmonaire obstructive chronique, d'asthme et de goutte. Le traitement pour des groupes spécifiques de patients est également considéré.

The pharmacologic treatment of essential hypertension continues to evolve as new agents are introduced and additional clinical trials are completed. This article reviews the 1989 recommendations of the Canadian Hypertension Society (CHS)¹ in the light of this new information. The new recommendations are an addition to those previously published on the nonpharmacologic management of blood pressure, which are unchanged.² When a diagnosis of hypertension has been made,³ the goal of reducing the diastolic blood pressure to less than 90 mm Hg is unchanged.⁴

This report was prepared by an expert panel appointed by the CHS. It has been reviewed in plenary session, and its recommendations were approved by secret ballot at the 1992 consensus conference of the CHS. The

methods of critical appraisal of the research are described in more detail in the first⁵ and second³ articles in this series and in the article by Sackett.⁶ Table 1 shows the rating system applied to most of the journal articles evaluated by the expert panel. The recommendations were graded according to the level of evidence available (Table 2).

Initial monotherapy for uncomplicated essential hypertension

Thiazide diuretics and β -blockers

Efficacy: The 1988 Canadian consensus conference on the pharmacologic treatment of hypertension reviewed major clinical trials⁷⁻¹² of thiazide diuretics and β -blockers in monotherapy, in combined therapy or as part of multiple drug therapy; it recommended these drugs for initial therapy for uncomplicated essential hypertension. The trials were included in a recent meta-analysis of the effect of antihypertensive therapy on cerebrovascular accident (CVA) and coronary heart disease (CHD), which concluded that drug treatment reduced the incidence of CVA by 42% and of CHD by 14% over 2 to 3 years.¹³ The authors speculated that although the benefits of such therapy for CVA are achieved in this relatively short time, only 50% of the expected CHD events were prevented.

Since 1988 three studies on hypertension in older groups have confirmed the efficacy and safety of diuretics and β -blockers and have shown a marked and significant reduction in the risk of CVA.¹⁴⁻¹⁶ (These trials are discussed in more detail in the next article in this series.¹⁷) They have confirmed the finding of an earlier

European study that the treatment of hypertension reduces the risk of fatal and nonfatal CHD events,¹⁸ although in one of them, the British Medical Research Council trial, the diuretics but not the β -blockers were found to reduce the risk of CHD events.¹⁶ However, recent reports from the Metoprolol Atherosclerosis Prevention in Hypertension (MAPHY) study concluded that in hypertensive patients with diastolic blood pressures between 100 and 130 mm Hg a β -blocker — metoprolol — reduced the rates of cardiovascular events, including death, but a thiazide diuretic did not.^{19,20}

Safety: Recent studies have confirmed the conclusions of the earlier consensus conference¹ on the safety of thiazide diuretics. Hydrochlorothiazide, 25 mg daily, or its equivalent produces only small changes in the serum potassium level and has no arrhythmogenic effect. If, however, a higher dose is necessary for some reason other than hypertension (e.g., congestive heart failure) a potassium-sparing diuretic should be given along with the thiazide rather than potassium supplements.

The one concern about the safety of thiazide diuretics that remains open is their effect on levels of serum lipids.^{21–30} There is general agreement that higher doses (50 to 100 mg daily) of hydrochlorothiazide result in an increase of 5% to 10% in levels of low-density lipoprotein and total cholesterol with variable effects on levels of high-density lipoprotein (HDL) cholesterol, from a decrease of 30% to an increase of 10%. Because of methodologic differences among the studies we do not have a clear picture of the duration of the hyperlipidemia. The Oslo Study,²⁷ which measured lipid fractions

and included a control group, did not show a continued elevation of cholesterol levels. These studies leave unanswered a key question: Would the lower antihypertensive dosage of thiazides currently recommended (such as 25 mg daily of hydrochlorothiazide or its equivalent) cause similar adverse effects? One thiazide, indapamide, may not have adverse effects on serum lipids levels,^{28,29} possibly because of its relatively low dosage, 2.5 mg per day. It appears that loop diuretics, such as furosemide, have effects similar to those of the thiazides, whereas the potassium-sparing diuretics have no effect on lipid levels; however, these nonthiazide diuretics have been studied less extensively.

The effect of β -blockers on serum lipids has also been well studied.^{30–35} The nonselective β -blockers typically raise triglyceride levels by 30% to 40% and lower HDL levels by 5% to 20%. The β_1 -selective blockers appear to have similar effects, although perhaps less of an adverse effect on HDL levels. The β -blockers with intrinsic sympathomimetic activity, such as acebutolol, oxprenolol and pindolol, and those with combined β -blocking and α -blocking activity, such as labetalol, do not adversely affect lipid profiles.

In patients without other risk factors or target-organ damage a baseline lipid profile should be obtained to measure overall risk. If the lipid levels are normal they should be rechecked several months after treatment is started with a β -blocker or a diuretic. Patients showing new lipid abnormalities should be considered for a change to drugs that do not adversely affect lipid profiles, such as α -blockers, angiotensin-converting enzyme (ACE) inhibitors, β -blockers with intrinsic sympathomimetic activity, calcium entry blockers and centrally acting drugs.

Other drugs

Alpha-blockers, centrally acting drugs, ACE inhibitors and calcium entry blockers have been shown to reduce blood pressure in comparison with placebo, but there is no information on their ability to prevent the major end points of CHD and CVA.

Alpha-blockers: Alpha-blockers are not widely used in monotherapy for hypertension.³⁶ Short-acting (prazosin) or long-acting (terazosin and doxazosin) α -blockers cause vasodilation by blocking postsynaptic α_1 -adrenergic receptors. These drugs may be used in initial

Table 1: Levels of evidence for rating studies of treatment, prevention and quality assurance

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

Table 2: Grading system for recommendations

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

monotherapy when others are contraindicated or ineffective, and they may be used in combination therapy with drugs from any other group, such as diuretics, β -blockers, centrally acting agents, ACE inhibitors and calcium entry blockers. Because α -blockers have neutral or beneficial effects on serum lipid levels and glucose homeostasis they may be beneficial in hypertensive patients with hyperlipidemia and diabetes mellitus. The risk of first-dose orthostatic hypotension can be reduced if small doses at bedtime are used initially or if the longer-acting drugs are used. Dizziness, loss of energy and nasal stuffiness are other adverse effects.

Centrally acting drugs: These drugs (methyldopa and clonidine) are generally recommended as alternatives for initial monotherapy in uncomplicated hypertension and for monotherapy in patients with coexisting medical conditions or target-organ damage. Adverse effects on the central nervous system often limit their use. These agents can be used for monotherapy in hypertension during pregnancy. Since they have neutral effects on serum lipid levels and glucose homeostasis they may be useful in patients with hyperlipidemia or diabetes. Methyldopa therapy has been associated with reversal of left ventricular hypertrophy.

Direct-acting vasodilators: Because they induce reflex tachycardia and sodium and water retention the direct-acting vasodilators hydralazine and minoxidil are generally used in combination with thiazide diuretics and β -blockers. Both drugs have been associated with failure to reverse left ventricular hypertrophy and may even augment it. Hydralazine in combination with isosorbide dinitrate is an alternative for patients with congestive heart failure when ACE inhibitors cannot be used. Hydralazine in combination with a β -blocker can be used to treat hypertension during pregnancy.

ACE inhibitors and calcium entry blockers: The ACE inhibitors (e.g., captopril, enalapril, fosinopril, lisinopril and quinapril) are approved in Canada for the treatment of hypertension, and relatively large-scale clinical trials have suggested that they are effective in monotherapy or in combination therapy with a diuretic.³⁷⁻⁴⁰ The calcium entry blockers verapamil and diltiazem and the dihydropyridines in sustained-release formulations, such as nifedipine and felodipine, are also reasonably well tolerated and effective in monotherapy or in combination therapy with a diuretic or other drugs.^{37,39-42} In the patient with uncomplicated hypertension none of these agents causes clinically important biochemical abnormalities, and most studies show that they have no adverse effects on serum lipid levels.²⁹⁻³⁴

Patients with renal parenchymal disease, bilateral renal artery stenosis or congestive heart failure treated with diuretics may exhibit a deterioration in renal function with ACE-inhibitor therapy. The first dose of the ACE inhibitor, particularly captopril, has been associated with an abrupt fall in blood pressure that is most likely to occur in patients previously rendered hypo-

volemic by diuretic therapy. Disorders of taste and a rash occasionally occur. A prominent reason for discontinuing ACE-inhibitor therapy has been a dry cough, which affects 2% to 10% of patients. Angioneurotic edema is a rare but dangerous adverse effect. Hyperkalemia during ACE-inhibitor therapy may occur in patients with renal insufficiency, in diabetic patients with even mild renal impairment and in patients taking potassium supplements or potassium-sparing diuretics.

Verapamil and diltiazem may interfere with atrio-ventricular conduction, particularly in patients with pre-existing heart block. In vitro all calcium entry blockers exhibit negative inotropism, but this property does not appear to cause significant impairment in left ventricular performance unless severe generalized myocardial hypokinesia is present. All of the calcium entry blockers can cause constipation, edema, flushing and headache. The dihydropyridine calcium entry blockers are more likely to cause flushing and edema, whereas verapamil more commonly causes constipation. Most practitioners prescribe sustained-release preparations of calcium entry blockers, expecting fewer adverse effects and improved compliance. The concurrent use of β -blockers may minimize the occurrence of the unwanted side effects of dihydropyridine preparations.

Calcium entry blockers have been shown in animal models and in-vitro studies to have several antiatherosclerotic actions.⁴³⁻⁴⁵ In clinical studies coronary angiography showed that nifedipine⁴⁶ and nicardipine⁴⁷ caused regression of early minimal lesions. Neither study showed regression or changes in the progression of pre-existing lesions, and in fact a higher rate of death was found in the group treated with nifedipine.⁴⁸ Studies of secondary prevention with calcium entry blockers after a first myocardial infarction have indicated that verapamil and diltiazem are effective only if given to patients without left ventricular dysfunction.^{49,50} Dihydropyridines such as nifedipine may adversely affect outcome in patients suffering a myocardial infarction, irrespective of the functional status of the left ventricle.⁵¹ This is in direct contrast to the established secondary preventive effects of β -blockers and (reported more recently⁵²) acebutolol after myocardial infarction.

Several in-vitro studies have confirmed that ACE inhibitors have antiatherosclerotic actions.⁵³⁻⁵⁵ Captopril has decreased aortic atherosclerosis in animal models,^{44,45} although the potential clinical benefit has not been assessed. There is ample evidence that ACE inhibitors provide substantial benefit to patients with congestive heart failure,⁵⁶ but this evidence cannot be applied to patients with hypertension.

As noted previously, the role of diuretics and β -blockers in initial therapy for mild or uncomplicated hypertension is well supported. The actions of ACE inhibitors and calcium entry blockers appear to be comparable, and some practitioners argue for the addition of these other drug groups to diuretics and β -blockers for

initial monotherapy, with the expectation of improved outcome for cardiovascular disease. Unfortunately, not enough long-term clinical trials have been done with the main end points of illness or survival rates to conclude that these drugs may be recommended along with diuretic or β -blocker therapy. If the newer drug groups prove not to be as effective as diuretic or β -blocker therapy in preventing stroke, for example, any reduction in the incidence of cardiovascular disease or any improvements in longevity could be offset. Other purported attributes of the newer compounds, such as favourable effects on the quality of life and neutral effects on serum lipid levels, have not as yet been related to improvements in long-term rates of illness and death. Consequently, decisions to favour one treatment over the other remain speculative.

Overall there has been a trend to use lower doses even for the newer compounds, such as the ACE inhibitors. Some believe that ACE inhibitors produce fewer short-term side effects than diuretics, β -blockers or calcium entry blockers, but there is no strong evidence for this contention. As well, recommending therapy with ACE inhibitors or calcium entry blockers for the initial treatment of uncomplicated hypertension would carry considerable cost implications.

Nevertheless, since the drug groups have different profiles of adverse effects the availability of these newer agents offers the physician options for individualizing therapy when the drug of first choice proves ineffective or produces unacceptable side effects.

Improvement in the quality of life

One of the proposed advantages that the newer agents, especially the ACE inhibitors, have over the diuretics and β -blockers is that they produce fewer negative effects on subjective measurements of quality of life. The adverse effects of ACE inhibitors have not substantially altered since the previous consensus conference, but more information has become available on the assessment of quality of life, adverse effects and the differences between ACE-inhibitor classes and other, traditional antihypertensive drug classes. In the past several years, after the landmark study of Croog and colleagues,⁵⁷ some reports have suggested that ACE inhibitors may be associated with fewer effects on quality of life than propranolol⁵⁸ but not other β -blockers, such as atenolol.⁵⁸⁻⁶⁰

A recent meta-analysis of nine trials⁶¹ included 1620 patients given drugs from six drug groups and examined changes in sexual function, sleep, psychomotor performance, general well-being and mood. A small overall benefit of treatment was found for all constructs except sexual function, which was not adversely affected. Overall, ACE inhibitors, calcium entry blockers, diuretics and β -blockers improved the quality of life, whereas centrally acting agents and direct-acting va-

sodilators showed no treatment or adverse effects. A small positive effect on general well-being was seen with ACE inhibitors, and mood was slightly improved by ACE inhibitors, diuretics and β -blockers. No negative effects were detected for any construct with any drug group. The authors commented that, although none of the drug groups had a clearly superior effect on the quality of life, tailoring drug treatment could improve the outcome for a given patient.

Recommendations

The recommendations are summarized in Table 3, and lists of commonly used antihypertensive agents are given in Table 4; the lists of drugs or drug groups for monotherapy are in alphabetical order when there is no preferred order.

If there are no coexisting medical conditions or target-organ damage the following recommendations for the pharmacologic treatment of essential hypertension will apply.

Recommendation 1: Initial therapy should be monotherapy with either a low-dose thiazide diuretic (e.g., hydrochlorothiazide, 25 mg daily) or a β -blocker (grade A).

Recommendation 2: If the response is inadequate or there are adverse effects, substitute the alternative drug (grade A).

Recommendation 3: If there is a partial response, consider a combination of a diuretic and a β -blocker (grade A) or monotherapy with an α -blocker, ACE inhibitor, calcium entry blocker or centrally acting drug (grade B).

Recommendation 4: If there is an adverse effect or a contraindication to diuretic and β -blocker therapy, consider monotherapy with one of the other groups of drugs (grade B).

Recommendation 5: If the blood pressure is still not controlled, try combinations such as a low-dose diuretic with an ACE inhibitor, a calcium entry blocker, a centrally acting drug or an α -blocker (grade B).

Recommendation 6: Alternatively, a β -blocker could be given with a vasodilator (such as a dihydropyridine calcium entry blocker), hydralazine or an α -blocker (grade B).

Recommendation 7: Other combinations may be indicated (grade B/C).

Recommendation 8: Resistant hypertension may require combinations of three or more drug groups (grade C). Consider possible reasons for the poor response to therapy, such as noncompliance or secondary causes of hypertension, including consumption of other drugs.

Since a significant proportion of patients with mild hypertension have associated risk factors, such as an abnormal lipid profile, raised blood glucose or insulin levels, or left ventricular hypertrophy⁶² and since this proportion increases as levels of blood pressure rise,⁶³ it can be argued that we should use drug therapy that not only lowers blood pressure but is also known to ameliorate or to not aggravate associated risk factors for cardiovascular events. Certainly, when other medical conditions and cardiovascular risk factors coexist with hypertension the α -blockers, ACE inhibitors, calcium

entry blockers and centrally acting drugs can be considered as alternatives for initial monotherapy.

Recommendation 9: For hypertensive patients with coexisting medical conditions or target-organ damage, drug treatment should be individualized to obtain maximum benefit with minimum risk. The beneficial and adverse effects of specific drugs on associated risk factors should also be considered (grade D).

Concurrent cardiovascular disease

Ischemic heart disease:

Recommendation 10: For patients with angina and hypertension, use β -blockers (grade B).

Recommendation 11: Alternatively, calcium entry blockers such as diltiazem and verapamil may be prescribed for monotherapy (grade B). A dihydropyridine calcium entry blocker should generally be combined with a β -blocker but may be prescribed for monotherapy (grade B).

Recommendation 12: For patients with hypertension and a previous myocardial infarction β -blockers offer protection against reinfarction and death (grade A).

Recommendation 13: The calcium entry blockers verapamil and diltiazem but not dihydropyridines have been shown to reduce the risk of cardiovascular complications if left ventricular function is not impaired (grade A).

Congestive heart failure: The treatment of hypertension in patients with congestive heart failure should generally include diuretics or ACE inhibitors or both. Furosemide is recommended as the diuretic of choice if

salt and water retention requires therapy. The ACE inhibitors are specifically recommended for the treatment of congestive heart failure with or without hypertension and are generally administered in combination with digoxin and furosemide. Hydralazine combined with isosorbide dinitrate has been shown to be effective in the treatment of heart failure and may be considered if ACE inhibitors are contraindicated or not tolerated. Low-dose β -blocker therapy in patients with severe congestive cardiomyopathy is currently under investigation. However, these patients are usually not hypertensive.

Recommendation 14: Diuretics and ACE inhibitors are first-line therapy (grade A).

Recommendation 15: A combination of hydralazine and isosorbide dinitrate can be considered as alternative therapy if ACE inhibitors cannot be used (grade A).

Recommendation 16: Beta-blockers or calcium entry blockers are not recommended for patients with severe left ventricular systolic dysfunction (grade C).

Peripheral vascular disease: The symptoms of severe peripheral vascular disease may be exacerbated by the use of β -blockers, especially of the nonselective type. However, β -blockers may be used in most patients with mild peripheral vascular disease accompanied by intermittent claudication.^{64,65} Patients with hypertension and coexisting collagen vascular disease with Raynaud's phenomenon may benefit from treatment with vasodilators.

Recommendation 17: Beta-blockers may be used for patients

Table 3: Recommendations for the initial drug treatment of essential hypertension

Problem	Drug(s)
Essential hypertension without coexisting medical conditions or target-organ damage	Low-dose thiazide diuretic or β -blocker
Partial response to monotherapy with diuretics and β -blockers	Combined diuretic and β -blocker or monotherapy with an α -blocker, angiotensin-converting enzyme (ACE) inhibitor, calcium entry blocker or centrally acting drug
Adverse effects of or contraindication to diuretics or β -blockers	Other monotherapy as above
Essential hypertension with coexisting medical conditions or target-organ damage	Monotherapy as appropriate
Inadequate response. Coexisting medical conditions or target-organ damage may determine the choice.	Diuretic with an ACE inhibitor, calcium entry blocker, α -blocker, other vasodilator or a centrally acting drug
	β -blocker with a dihydropyridine calcium entry blocker, α -blocker, other vasodilator or centrally acting drug
Adverse effects of or contraindication to diuretics or β -blockers	ACE inhibitor and calcium entry blocker or other combination

with mild peripheral vascular disease, but they may aggravate the symptoms of severe disease (grade B).

Recommendation 18: In patients with Raynaud's phenomenon vasodilators may be of benefit (grade B/C), but β -blockers are contraindicated (grade B/C).

Cardiovascular risk factors

Dyslipidemia:

Recommendation 19: Patients with abnormal lipid levels are at increased risk of cardiovascular complications. Dyslipidemia should be treated in accordance with current guidelines (grade A).

There is a concern that some antihypertensive drugs that adversely affect lipid levels could have a deleterious effect in these patients. However, according to the evidence from clinical trials, drugs such as diuretics and β -blockers reduce long-term rates of illness and death despite reported negative effects on lipid profiles.

Recommendation 20: In the setting of dyslipidemia α -blockers, ACE inhibitors, β -blockers, calcium entry blockers, centrally acting agents and low-dose thiazide diuretics may all be considered for monotherapy (grade D).

Recommendation 21: Since β -blockers without intrinsic sympathomimetic activity may worsen lipid profiles β -block-

Table 4: Commonly used antihypertensive drugs

Drug*	Daily dose, mg	
	Starting	Full
Thiazide diuretics		
Chlorthalidone (Hygroton)	12.5	25
Hydrochlorothiazide (HydroDiuril, Esidrix)	25	50
Indapamide (Lozide)	2.5	2.5
Metolazone (Zaroxolyn)	2.5	5
Beta-blockers		
Acebutolol (Monitan, Sectral) (S)	200	800
Atenolol (Tenormin)	50	100
Labetalol (Trandate)	200	1200
Metoprolol (Lopresor, Betaloc)	50	200
Nadolol (Corgard)	40	160
Oxprenolol (Trasicor) (S)	80	320
Pindolol (Visken) (S)	10	30
Propranolol (Inderal)	80	320
Timolol (Blocadren)	10	40
ACE inhibitors		
Captopril (Capoten)	25	100
Enalapril (Vasotec)	10	40
Lisinopril (Prinivil, Zestril)	10	40
Quinapril (Accupril)	10	40
Calcium entry blockers		
Diltiazem (Cardizem)	180	360
Felodipine (Plendil, Renedil) (V)	5	20
Nicardipine (Cardene) (V)	60	120
Nifedipine (Adalat) (V)	20	80
Verapamil (Isoptin)	240	480
Centrally acting drugs		
Clonidine (Catapres)	0.2	1.2
Methyldopa (Aldomet)	500	2000
Reserpine (Serpasil)	0.1	0.25
Alpha-blockers		
Doxazosin (Cardura)	1	16
Prazosin (Minipress)	1	20
Terazosin (Hytrin)	1	20
Direct-acting vasodilators		
Hydralazine (Apresoline) (V)	50	200
Minoxidil (Loniten) (V)	5	20
Combinations		
Hydrochlorothiazide/amiloride (Moduret)		
Hydrochlorothiazide/atenolol (Tenoretic)		
Hydrochlorothiazide/enalapril (Vaseretic)		
Hydrochlorothiazide/spironolactone (Aldactazide)		
Hydrochlorothiazide/timolol (Timolide)		
Hydrochlorothiazide/triamterene (Dyazide)		

*(S) = sympathomimetic activity, (V) = vasodilator.

ers with intrinsic sympathomimetic activity should be considered when β -blockade is required (grade B).

Recommendation 22: Alternatively, α -blockers, calcium entry blockers, ACE inhibitors and centrally acting drugs, which do not adversely affect lipid levels, can be considered (grade B).

Recommendation 23: High doses of thiazides adversely affect lipid levels. Doses that are more than the equivalent of 50 mg daily of hydrochlorothiazide are not indicated for the treatment of hypertension (grade D). There are insufficient data to make a definitive statement about the effect on lipids of low-dose thiazide therapy (e.g., hydrochlorothiazide, 12.5 to 25 mg daily), especially in the long term.

Recommendation 24: If lipid status is a special concern, monitor the patient for several months after starting treatment and change to a drug that does not adversely affect lipid levels if clinically important changes occur (grade D).

Left ventricular hypertrophy: Left ventricular hypertrophy is commonly associated with hypertension and is an independent risk factor and predictor for cardiovascular disease and sudden death.⁶⁶ As outlined in a recent meta-analysis of 109 treatment studies,⁶⁷ evidence continues to accumulate demonstrating the effectiveness of monotherapy with ACE inhibitors, calcium entry blockers, β -blockers, methyldopa, α -blockers and diuretics (thiazide, chlorthalidone and indapamide) in reducing the echocardiographically calculated left ventricular mass. ACE inhibitors had the most pronounced effect on mass and wall thickness; β -blockers and calcium entry blockers were slightly less useful. The effect of diuretics on calculated mass was considered to be due primarily to a reduction in the internal diameter of the left ventricle, since wall thickness was little altered.

Several caveats need to be mentioned regarding this meta-analysis. Only 18 (17%) of the 109 studies were randomized, double-blind, parallel-group comparisons; the rest were single-blind or open studies. Excluding placebo and nonpharmacologic therapy, each drug-treatment group had an average of only 15.7 patients, who were followed up for an average of only 8.4 months. Differences in age may have confounded the results. The relevance of a reduction in calculated left ventricular mass obtained through a decrease in wall thickness (as a result of therapy with ACE inhibitors, calcium entry blockers or β -blockers) as compared with a decrease in internal diameter (as a result of therapy with diuretics) is unknown.

Although it may be appealing to recommend ACE inhibitors for initial therapy because of their greater potential to reverse left ventricular hypertrophy compared with calcium entry blockers and β -blockers, there is no evidence that the regression in left ventricular mass associated with this therapy is followed by a reduced incidence of cardiovascular events, including sudden death. Clearly, at present there is no support for a particular agent to be chosen for initial therapy because of its ability to prevent or reverse left ventricular hypertrophy. However, since electrocardiographic detection of this

condition, although specific, is not very sensitive and echocardiographic detection is sensitive and specific but expensive as well as difficult to validate in all laboratories, the presence of left ventricular hypertrophy in the hypertensive population remains underdiagnosed.³

Recommendation 25: Left ventricular hypertrophy is a significant risk factor for cardiovascular complications (grade C). Its reversal has not been proven to reduce rates of cardiovascular events. There is insufficient evidence to base initial therapy on the reported effects of drugs on left ventricular hypertrophy.

Recommendation 26: Most antihypertensive drugs reduce left ventricular hypertrophy; the exceptions are arteriolar vasodilators, such as hydralazine or minoxidil, which can increase it (grade B/C).

Diabetes mellitus: The use of diuretics has been noted previously to worsen glucose intolerance. This was thought to have been related to the hypokalemic suppression of insulin release, but new reports^{68,69} have suggested that thiazide diuretics and β -blockers induce a state of insulin resistance and that their use is associated with an increase in serum insulin concentrations. This insulin resistance is associated with lipid disturbances, but the long-term impact is as yet unclear. ACE inhibitors and perhaps calcium entry blockers as well as α -blockers are thought to have no adverse effects and may have beneficial effects on insulin resistance.^{68,70}

The recommendations on the treatment of hypertension in patients with diabetes presented in the last article in this series⁷¹ should be followed.

Tobacco smoking:

Recommendation 27: Cigarette smoking is an important cardiovascular risk factor (grade C). Hypertensive patients should be encouraged to quit smoking.

Recommendation 28: The benefit of β -blocker therapy in smokers, particularly the elderly, is uncertain (grade B).

Other coexisting medical conditions

Chronic obstructive pulmonary disease:

Recommendation 29: Patients with chronic obstructive pulmonary disease should avoid β -blockers (grade C). ACE inhibitors can cause a chronic dry cough, which can be confused with chronic respiratory disorders. Discontinuation of therapy is usually required to eliminate the cough.

Asthma:

Recommendation 30: For patients with reversible airway disease all β -blockers are contraindicated (grade C).

Recommendation 31: For patients taking β_2 -adrenoceptor agonists (e.g., salbutamol), which reduce serum potassium levels, a combination of a potassium-sparing diuretic and a thiazide should be used for initial therapy (grade D).

Gout: Thiazide diuretics may cause hyperuricemia

and gout. If a diuretic is essential for the control of hypertension, gout can often be prevented by the concurrent use of allopurinol. In the absence of gout or urate stones hyperuricemia alone does not require allopurinol therapy and is not a contraindication to thiazide diuretic therapy.

Recommendation 32: In general, thiazide diuretics should be avoided (grade C).

Recommendation 33: Asymptomatic hyperuricemia is not a contraindication to diuretic therapy.

Special patient status

Pregnant: Hypertensive patients who become pregnant may require withdrawal of antihypertensive therapy during the first trimester because of a natural decline in blood pressure during this period. Clinical studies support the use of methyl dopa or β -blockers (e.g., atenolol, metoprolol and labetalol) for the control of hypertension in pregnancy. Clonidine may also be used. The ACE inhibitors and calcium entry blockers are teratogenic, so use of these agents should be avoided during pregnancy. When used in the second or third trimester of pregnancy ACE inhibitors can also cause fetal injury and death. Low-dose acetylsalicylic acid has been suggested as prophylaxis against pregnancy-induced hypertension.⁷² However, further trial evidence is required. The effect of calcium and magnesium supplementation is also under investigation.^{73,74}

Recommendation 34: Methyl dopa, clonidine, hydralazine and β -blockers (e.g., atenolol, metoprolol, oxprenolol and labetalol) may be used alone or in combination (grade B/C).

Recommendation 35: In general, because of their teratogenicity ACE inhibitors should not be prescribed for women capable of childbearing. When used in the second or third trimester of pregnancy ACE inhibitors can cause fetal injury and death and are therefore contraindicated (grade C).

Recommendation 36: In general, calcium entry blockers should not be prescribed for women capable of childbearing because of teratogenicity (grade C).

Black: The prevalence of hypertension and its complications is considerably higher in black patients than in the white population. Diuretics have generally been considered to be more effective than β -blockers in treating hypertension in black patients, although a β -blocker in combination with a diuretic may be useful in both black and white individuals. In a recent review of comparative trials of antihypertensive therapy in black patients⁷⁵ the authors concluded that calcium entry blockers were as effective as hydrochlorothiazide and more effective than β -blockers or ACE inhibitors. This does not preclude the use of β -blocker or ACE-inhibitor therapy in black patients.

Recommendation 37: Thiazides in low doses are recommended over β -blockers (grade B).

Recommendation 38: Calcium entry blockers are as effective

as diuretics (grade B) and may be more so than β -blockers or ACE inhibitors (grade B).

With renal disease: Hypertensive nephropathy is defined as renal insufficiency for which arterial hypertension has been identified as the only cause. The proportion of hypertensive patients whose renal disease progresses to end-stage is unclear, although US data point to an increase in the proportion of patients with hypertensive nephropathy entering dialysis programs (white patients: 0.36 to 0.62 per 100 000 population; black patients: 6.4 to 9.6 per 100 000 population).⁷⁶

The groups of patients at greatest risk of chronic renal failure due to or in association with hypertension are black people, elderly people (more than 60 years of age) and patients with higher diastolic pressures.⁷⁷⁻⁸¹ Any patient with primary renal disease or renal disease secondary to another condition, such as diabetes, is likely to experience accelerated deterioration in renal function with coexistent hypertension.^{82,83}

No prospective studies have addressed the "ideal" blood pressure for the hypertensive patient with renal disease. One study compared the rate of deterioration of renal function in patients with essential hypertension with that of patients with "normal blood pressure" and found that renal function deteriorated regardless of blood pressure level and that deterioration may not be avoidable, only limited.⁸⁴ In retrospective studies a blood pressure of 140/90 mm Hg appears to be the breakpoint above which renal function deteriorates faster.⁸²⁻⁸⁶ This suggests that blood pressure should be reduced below 140/90 mm Hg. Both black and white patients benefit from adequate antihypertensive therapy, but as yet no particular drug or class of drugs can be recommended.^{62,63,84-88} The effect of a drug on proteinuria has not been proven to be an indicator of renoprotection. Selection of drug therapy can be guided by concomitant medical conditions and blood pressure response.

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