CHAPTER

55

Management of Hypertension – Changing Guidelines : Importance of Diuretics

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Introduction

Hypertension remains the most common risk factor for cardiovascular morbidity & mortality. Hypertension is among the most important preventable causes of death worldwide. The treatment of hypertension is a key strategy for primary prevention of cardiovascular disease (CVD).

Debate has been going on for several years about whether the mortality and morbidity benefits of treating hypertension with drugs can be attributable exclusively to the reduction in risk from lowering blood pressure per se, or whether certain drugs confer additional CV benefits owing to effects not directly associated with their antihypertensive efficacy. In particular, the claims that interfering with the renin-angiotensin system might be beneficial in patients at risk has been widely discussed.

Despite massive efforts to identify and treat hypertension less than a third of individuals with a usual BP exceeding 140/90 mmHg are adequately treated. Even in individuals whose hypertension is well controlled less than a third are protected from subsequent strokes and heart attacks. With the recognition that risk increases linearly even in high-normal ranges in BP the need for assessment going beyond BP values and using individuals absolute overall CV risk as the criterion for therapy has become obvious.

Changing Guidelines

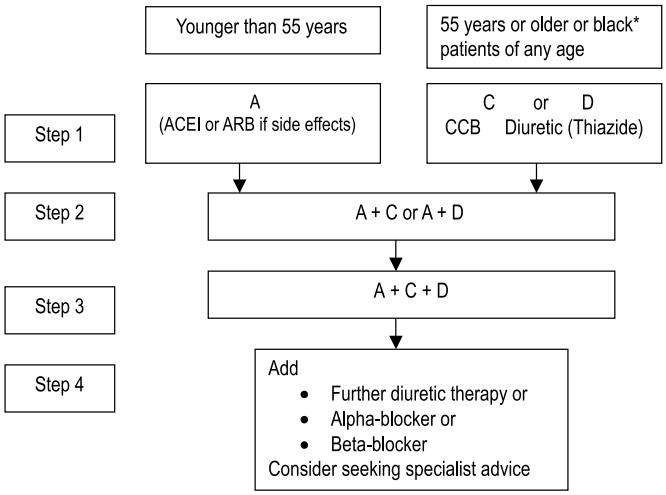
International guidelines like Joint National Committee 7th Guidelines from US, World Health Organization /International Society of Hypertension Guidelines, European Society of Hypertension/ European Society of Cardiology 2003 and 2007 Guidelines for the Management of Arterial Hypertension are discussed briefly focusing on important issues including the current role for diuretics.

JNC 7 – Report

Diuretics were preferred as initial therapy of hypertension in every JNC report since 1984 until 2003. For uncomplicated hypertension, thiazide diuretic should be used for most, either alone or combined with drugs from other classes. Two or more antihypertensive medications will be required to achieve goal BP of < 140/90 mm/Hg , or < 130/80 mm/Hg for patients with diabetes and chronic kidney disease. For patients whose BP is more than 20 mmHg above the systolic BP goal or more than 10 mmHg above the diastolic BP goal, initiation of therapy using two agents, one of which usually will be a thiazide diuretic, should be considered.

All trials taken together suggest broadly similar cardiovascular protection from BP–lowering with ACEIs, CCBs, and ARBs, as with thiazide–type

Table 1 : Algorithm: treatment of newly diagnosed hypertension



British Hypertension Society Royal College of Physicians

diuretics and BBs, although some specific outcomes may differ between the classes.

WHO/ISH Committee Report

World Health Organization /International Society of Hypertension committee (1) recommend that diuretics should be considered as first choice in the treatment of hypertension not complicated by other conditions.

British Hypertension Society guidelines

Now there is much interest in the updated recommendations for the drug treatment of hypertension issued by the UK's National Institute for Health and Clinical Excellence (NICE) working in collaboration with the British Hypertension Society (BHS).

NICE guidelines developers acknowledged the evidence base for treating hypertension in older people (> 55 years) with established vascular disease. The guideline highlighted an alarming absence of data about the best treatment of hypertension in younger people (< 55 years). It recognized that, in older people lowering BP efficacy is pre-eminent in driving treatment benefits and that the two most clinically cost-effective drug classes for initial lowering of blood pressure, in this age group, are calcium-channel blockers or a thiazide-type diuretic. Because blood pressure in older people is more resistant to therapy as a result of attendant vascular and target organ damage, the need for two or more drugs in most people was acknowledged with recommendation at step 2 to combine calcium-channel blockers or thiazide-type diuretic with an angiotensin receptor blocker (if the angiotensin-converting-enzyme inhibitor is not tolerated). At step 3, the combination of angiotensin-converting-enzyme inhibitor + calcium-channel blockers + thiazide-type diuretic was recommended. These logical drug combinations are presented in a simple algorithm (Table 1).

What to do about younger people with hypertension? Without hard clinical endpoint data for younger people, NICE/BHS justifiably downgraded the evidence rating for the treatment of younger people and resorted to a surrogate for treatment benefit, notably efficacy in BP lowering. Conclusion was that for younger people an ACEI was likely to be a more effective initial therapy than CCB or thiazide-type diuretics.

2007 Guidelines for the Management of Arterial Hypertension

For several years the European Society of Hypertension (ESH) and the European Society Cardiology (ESC) decided not to produce their own guidelines on the diagnosis and treatment of hypertension but to endorse the guidelines on hypertension issued by the WHO and ISH.

However, In 2003, the decision was taken to publish ESH/ESC specific guidelines[3] because, WHO/ISH Guidelines are applicable only to developing countries and poor nations.

However, since 2003, considerable additional evidence on important issues related to diagnostic and treatment approaches to hypertension has become available and therefore updating of the previous guidelines has been found advisable.

Pharmacological therapy

Choice of antihypertensive drugs

The large number of randomized trials of antihypertensive therapy, both those comparing active treatment versus placebo and those comparing treatment regimens based on different compounds, confirm the conclusion of the 2003 ESH/ESC Guidelines[2] that A) the main benefits of antihypertensive treatment are due to lowering of blood pressure per se, and are largely independent of the drugs employed, and B) thiazide diuretics [as well as chlorthalidone and indapamide], ß-blockers ,calcium antagonists, ACE inhibitors and angiotensin receptor antagonists can adequately lower blood pressure and significantly reduce CV outcomes. Therefore all these drugs are suitable for the initiation and maintenance of antihypertensive treatment either as monotherapy or in some combinations with each other. Each of the recommended classes may have specific properties, advantages and limitations.

Identification of the first class of drugs to be used in the management of hypertension has always been a debated issue. However , there is now conclusive evidence from trials that combination treatment is needed to control blood pressure in the majority of patients.[3]

Diuretics

In hypertension, diuretics continued to be used as first–line therapy, although in much lower doses – a position supported by recent meta–analysis.[4,5]

The benefit / risk ratio is high in CHF. In hypertension, their use has been questioned because of certain blood biochemical changes following diuretic therapy. Nevertheless, they retain their primacy as first–line agents when used in low daily doses, such as 12.5 to 25 mg of hydrochlorothiazide, that reduce total and cardiovascular mortality, stroke, coronary heart disease, and congestive heart failure.[4] Higher doses, 50 to 200 mg, as used in the past, did not reduce coronary heart disease nor total mortality. The value of diuretics is particularly well established in certain groups of hypertensive patients – the elderly, the obese, and blacks- and those already receiving ACIs or ARBs. Further more, low doses of diuretics can be given over prolonged periods with minimal changes in blood lipids, glucose, and potassium.

Loop Diuretics

Furosemide

In hypertension, twice daily low–dose furosemide can be effective even as monotherapy or combined with other agents and is increasingly needed as renal function deteriorates. In hypertensive crisis, intravenous furosemide is used if fluid overload is present. It is widely believed that in severe renal failure high dose furosemide increases the GFR.

Torsemide

This loop diuretic has a longer duration of action than Furosemide. In U.S the only doses registered for antihypertensive efficacy are 5 to 10 mg daily.

Thiazide Diuretics

Thiazide diuretics remain the most widely recommended first–line therapy for hypertension,[6] Lower doses with fewer biochemical alterations provide full antihypertensive as shown in several large trials. The response rate in hypertension to thiazide monotherapy is variable and may be disappointing, being only about 45% on one trial with 12.5 to 25 mg chlorthalidone daily.[7] With hydrochlorothiazide, the full antihypertensive effect of low-dose 12.5 mg daily may take up to 6 weeks.

Combination therapy for example, with an ACE inhibitor or ARB becomes preferable rather than increasing the dose beyond 25 mg daily[8] or even beyond 12.5 mg daily.[9] Chlorthalidone was chosen for two most important trials – SHEP and ALLHAT.[7] Chlorthalidone lasts longer[8] and no more than 15 mg should be used. Hydrochlorothiazide 12.5 mg is a good alternative.

Indapamide

Indapamide (Natrilix) is a thiazide–like diuretic

although with a different indoline structure. It has two properties beyond diuresis. First, there is added vasodilation.[10] A second unusual property is a high concentration class I and III antiarrhythmic effect.[11] Indapamide has a terminal half life of 14 to 16 hrs.

With a reduced but still antihypertensive dose of only 0.625 to 1.25 mg combined with the ACE inhibitor perindopril 2-4 mg, the serum potassium fell by only 0.11 mmol/L over 1 year and the blood glucose was unchanged from placebo.[12] Regarding regression of LV hypertrophy , indapamide was better than enalapril in the LIVE study (LVH with indapamide vs enalapril).[13]

Spironolactone and Eplerenone

Spironolactone and Eplerenone are both aldosterone antagonists and potassium sparers. Eplerenone provided additional benefit in the large EPHESUS trial of post MI patients by further reducing mortality.[14] Eplerenone was also as effective as enalapril, 40 mg daily, in regressing LVH and lowering blood pressure.[15] It would become a primary drug for treatment of hypertension, as well as a mortality reducer in CHF and in post infarct patients. Cost is prohibitive. These aldosterone receptor blockers are also useful in the treatment of primary aldosteronism and in patients with resistant hypertension.[16]

Efficacy of Diuretics as Monotherapy and as Combination therapy

From evidence to Practice

A logical combination is that of an ACEI or ARB with low-dose thiazide, for example, low–dose perindopril with low–dose indapamide.[12] Thiazide diuretic increase renin levels and ACEIs or ARBs decrease the metabolic side effects of thiazides.

Ageing and Isolated Systolic Hypertension [ISH]

The systolic blood pressure increases with age as the aorta stiffens. This systolic upswing is world wide. The JNC VII guidelines, which have been endorsed by several professional organizations, including the American Medical Association, and the American Society of Hypertension, recommend thiazide–type diuretics as initial drug therapy for most patients with isolated systolic hypertension unless there are specific contraindications for their use.[17]

The joint guidelines of the European Society for Hypertension and the European Society of Cardiology do not give preference to diuretics and recommend any of the five major classes of anti hypertensive drugs for the first-line therapy.[18] Recent guidelines from Great Britain argue against the use of both diuretics and beta-blockers for initial therapy and favor ACEIs, angiotensin–receptor blockers, or calcium channel blockers.[19] Despite some differences in recommendations, all of these guidelines emphasize that the major benefits of therapy are related to lowering blood pressure and controlling hypertension.

Calcium antagonists with ACEI versus thiazide diuretics and beta blockers

A recent meta-analysis revealed that Calcium antagonists provided a slightly better protection against stroke but showed a reduced ability to protect against the incidence of heart failure.

INVEST, showed equal incidence of CV events in patients with coronary heart disease in whom treatment was started with a calcium antagonist verapamil, combined with an ACE inhibitor or with a ß-blocker atenolol, combined with a diuretic.[20]

The ASCOT trial has more recently added further information on the comparative efficacy of treatment initiated by either a calcium antagonist (Amlodipine) or a conventional drug.[21] The Amlodipine based treatment resulted in a slightly greater blood pressure reduction accompanied by a significant reduction in stroke, cardiovascular and all cause mortality. As in most trials, the majority of ASCOT patients received combination therapy (calcium antagonist with ACE inhibition versus beta blocker with thiazide diuretic).

ACE inhibitors versus thiazide diuretics and beta blockers

It should be mentioned that trials comparing ACEIs versus betablockers with diuretics have not always given entirely consistent results. In the second Australian blood pressure study[22] hypertensive patients randomized to an ACEI had a reduced number of cardiovascular events compared with those randomized to thiazide diuretics, although the difference was small, only evident in men, and significant only if recurrent events were included. In the ALLHAT trial,[23] on the contrary, hypertensive patients on the diuretic chlorthalidone showed a similar incidence of coronary heart disease (the primary end point) as compared to those randomized to the ACEI lisinopril, but heart failure and stroke were significantly lower in the diuretic treated group (which also showed a greater blood pressure reduction).

Randomized trials based on intermediate endpoints

Two large studies have compared an ACE inhihitor-diuretic fixed combination (perindopril –indapamide) with the beta blocker atenolol and the ACE inhibitor enalapril, but the greater reduction of left ventricular mass with the combination was associated with a greater blood pressure reduction.[24,25] and significantly correlated with a greater reduction in central blood pressure.[26]

As to diuretics, the only adequately powered study[27] shows a significant efficacy of indapamide; the same study also showed a superiority of indapamide over the ACE inhibitor, enalapril. As this is the only study in which an ACE inhibitor was found not to induce left ventricular mass reduction, no conclusion can be drawn on the comparative efficacy of diuretics versus ACE inhibitors in regressing left ventricular hypertrophy.

Blood pressure in high risk patients

Data favoring lower blood pressure targets in patients in whom a high risk conditions is due to factors other than diabetes are of variable strength.

The most clear evidence concerns patients with previous stroke or transient ischemic attack, since in the PROGRESS study subjects with a history of cerebrovascular disease in whom treatment reduced blood pressure from 147/86 mmHg to 138/82 mmHg showed a 28% reduction in stroke recurrence and 26% reduction in the incidence of major cardiovascular events compared with placebo in which the blood pressure reduction was negligible. There were substantial cardiovascular benefits also in normotensive patients in whom on – treatment values were reduced to 127/75 mmHg. Further more, in a recent post – hoc analysis of the PROGRESS data a progressive reduction in the incidence of stroke recurrence (particularly hemorrhagic stroke) has been reported until achieved systolic blood pressure values of about 120 mmHg.[28]

Antihypertensive therapy in patients with renal dysfunction

To achieve the blood pressure goal, combination therapy of several antihypertensive agents (including loop diuretics) is usually required.

New onset diabetes

Almost all trials of antihypertensive therapy using new onset diabetes as an endpoint have shown a significantly greater incidence in patients treated with diuretics and /or ß-blockers compared with ACE inhibitors[22,23] angiotensin receptor antagonists or calcium antagonists. Therefore the claim that treatment induced and 'spontaneous' onset diabetes may be prognostically different appears impossible to confirm on confute.

Advantages of first–line combination in diabetic patients

Monotherapies have been shown to be ineffective in many patients, and delays in BP control significantly increase the risk of cardiac events, stroke, and death. In diabetic patients, in whom BP control is particularly hard to achieve, the use of

angiotensin–converting enzyme [ACE] inhibitors, has been recommended.

Consistent with these guidelines, comparative clinical trials have confirmed the value of the ACE inhibitor/diuretic combination treatment, perindopril /indapamide, in hypertensive diabetic patients and in patients with uncomplicated essential hypertension. Perindopril/indapamide has been shown to have an early and sustained effect on systolic BP and a specific and positive effect on the hemodynamics. Treatment attenuates after load on left ventricular myocardial hypertrophy, and myocardial oxygen consumption.

In diabetic patients with albuminuria, perindopril /indapamide treatment significantly reduces BP, the albumin excretion rate, and the urinary albumin/ creatinine ratio. The nephro protective effects of perindopril /indapamide remain significant after adjustment for changes in BP. Together; these data suggest that perindopril /indapamide combination, through its effect on BP lowering and target organ protection, is suitable for medical needs of a wide range of hypertensive patients including diabetic patients.

Benefits of perindopril and indapamide combination on micro-and macro circulation

Maintaining vascular health has become an important target in the management of cardiovascular disease and hypertension–related organ damage. The microvasculature, which is both a target and a determinant of hypertension, contributed to the pathological changes in the macrocirculation and subsequently to end organ damage.

The prevention or regression of hypertension dependent vascular alterations represent a desirable goal for pharmacological treatments. Combination treatment with ACE inhibitor diuretic, perindopril /indapamide , has been shown to have positive effects on the micro-and macro–circulation and on subsequent cardiovascular disease. In the REASON study, perindopril/indapamide treatment decreased measures of arterial stiffness and macrovascular health .These data suggest that hypertension–related damage to the micro-and macro–vascular system may be manageable through pharmacological interventions such as fixed–combination treatment perindopril/indapamide.

Summary

In hypertension, diuretics remain the best tested of the potential first line antihypertensive agents achieving better results when used in low doses. Being powerful therapeutic agents, they have the potential for major and serious side effects at higher doses. The benefit /risk ratio of diuretics in the therapy of mild hypertension has been particularly well documented. Patients with renal impairment also require a diuretic (loop or metolazone). For most hypertensive patients, a low dose thiazide diuretic , probably with a potassium-retaining component (amiloride, triamterene, spironolactone, or eplerenone) is appropriate. Thiazide diuretics combine well with ACEIs

Randomized controlled trials have conclusively proved the benefit of low dose diuretic either as mono therapy or as combination with other drugs like ACEI, ARB and CCBs for marked reduction of cardiovascular mortality or morbidity. However combination with beta blockers should be discouraged as this would potentiate the risk of developing new onset diabetes. International guidelines recommend the use of diuretics in elderly hypertensives, in people with isolated systolic hypertension and in blacks. Most recent guidelines approved combination therapy which included diuretic for achieving maximum benefit in cardiovascular protection.

Hypertension is the most important risk factor for cardiovascular morbidity and mortality. Hypertension is a preventable disorder. Treatment of hypertension is a key strategy for primary prevention of CVD. There are number of international guidelines like JNC VII, WHO/ISH guidelines ESH, ESC guidelines for managing arterial hypertension. Many guidelines have approved diuretics either as initiation or in combination with other antihypertensive therapy

based on evidence. There are number of trials using diuretics in the management of hypertension which confirmed its primary role. This article will cover the evidence, the guidelines and the role of diuretic in the management of hypertension.

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